Synthesis of 1-Azaspiro[4.4]nonane Derivatives Enabled by Domino Radical Bicyclization Involving Formation and Capture of Alkoxyaminyl Radicals

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Supporting Information

ABSTRACT: The application of a domino radical bicyclization for the synthesis of compounds containing the 1-azaspiro[4.4]nonane skeleton in 11−67% yields as a mixture of diastereomers is described (trans configuration preference). This process involved formation and capture of alkoxyaminyl radicals. For this purpose, O-benzyl oxime ethers with a brominated or iodinated aromatic ring or a terminal alkynyl group and an alkenyl moiety were employed as starting materials. The bicyclization was initiated by 2,2′-azobis(isobutyronitrile) or triethylborane and promoted by Bu₃SnH. The best results were obtained with O-benzyl oxime ethers containing an alkenyl moiety tethered to electron withdrawing groups or aryl substituents, whereas oxime radical precursor attached to methyl-substituted olefin precluded the capture of alkoxyaminyl radical, giving rise mainly to monocyclized product.

INTRODUCTION

Cephalotaxine represents the parent polycyclic core of a series of Cephalotaxus alkaloids, which are characterized for containing the 1-azaspiro[4.4]nonane ring system. These alkaloids exhibited potent antiproliferative activities against cancer cells.1a−c Particularly, homoharringtonine, an ester derivative of cephalotaxine, has been approved for treatment of chronic myeloid leukemia.1a,b In fact, 1-azaspiro[4.4]nonane derivatives are present in several compounds that exhibit marked biological activity, including inhibition of hepatitis C virus1d and as agonists of the nicotinic acetylcholine receptors (mACHR).1e,f From an ionic reactions approach, countless synthetic strategies have been described to build these spirane compounds, some of them compiled in the review of Tietze et al.2 published in 2004. Others have been reported until the end of 2018;3 among these, only one research group reports the construction of the aforementioned spirocycle in a single step, using a tandem intramolecular hydroamination/semipinacol rearrangement.4 On the other hand, in the field of radicals chemistry, there are only four synthetic methodologies reported in the literature: Bowman et al.5 used a domino bicyclization involving neutral aminyl radicals (Scheme 1), while Simpkins et al.,6 Renaud et al.,7a and Taniguchi and Ishisbashi7b carried out a synthetic route with alkyl radicals as intermediaries, starting from a pre-existing ring.

Scheme 1. First Approach via Radicals toward the Construction of 1-Azaspiro[4.4]nonane Derivatives

Our research group has been interested in the development of C−N bond-forming methodologies based on nitrogen-centered radical intermediaries using domino strategies to obtain heterocyclic compounds with biological potential. In that sense, we had previously reported a cascade radical bicyclization process involving oxime ethers, where aryl radicals were generated and immediately added onto a C==N bond in order to produce neutral alkoxyaminyl8 or alkyl-oxamyl9 radicals, which were then subsequently captured by a double bond activated with groups: Ph, CN, or CO₂Me. This process afforded heterocyclic compounds 5 exhibiting a pyrrolidine nucleus fused to the indene skeleton (Scheme 2),8 whereas 1,5 hydrogen transfer and 6-exo-trig cyclization occurred to produce the side products 6 and 7.

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On the basis of our research work, Landais et al.\textsuperscript{10} in 2008 attempted to obtain 1-azaspiro[4.4]nonane derivatives through the sequential formation and capture of neutral alkoxyaminyl radicals onto double bonds, but only monocyclized products were observed because nitrogen-centered radical intermediates underwent a recombination reaction with other carbon-centered radicals generated in the reaction media.

In order to exploit the synthetic potential of this methodology that allowed us to incorporate the nitrogen atom to fused ring systems with biological potential and also to avoid the above-mentioned side reactions, another class of precursors was designed. Thus, we preliminarily synthesized the oxime ether \textsuperscript{8} and when radical conditions were applied, the spiro[indene-1,2’-pyrrolidine] \textsuperscript{9} was obtained as a diastereomeric mixture (Scheme 3).\textsuperscript{11} In this case, during the domino bicyclization process, two rings were formed, connected by a single C atom (quaternary center) to generate the 1-azaspiro[4.4]nonane nucleus in a single stage reaction.

Therefore, on the basis of our previous research work, and taking into account that the synthetic potential of the alkoxyaminyl radicals has been far less explored, herein, we present a new methodology for the synthesis of 1-azaspiro[4.4]nonane-based compounds \textsuperscript{19} through a domino radical bicyclization from functionalized oxime ethers involving the formation and capture of alkoxyaminyl radicals.

**RESULTS AND DISCUSSION**

The radical precursors (oxime ethers) were synthetized in a four-stage route. Initially, the alkylation of methyl 3-oxobutanoate (methyl acetoacetate) was carried out on its most basic carbon through a dianion intermediate generating the \( \beta \)-ketoesters \textsuperscript{11−15},\textsuperscript{12} which were alkylated on the activated methylene. The carbomethoxy group (\( -\text{CO}_2\text{Me} \)) of the esters \textsuperscript{16a−c} was removed by dealkoxycarbonylation using the Krapcho reaction.\textsuperscript{13} Whereas the \( \beta \)-ketoesters \textsuperscript{16d−j} reacted under a novel modification\textsuperscript{14} to the aforementioned reaction affording ketones \textsuperscript{17d−j} (Table 1). Finally, the ester
16k was dealkoxycarbonylated using the Curran method\textsuperscript{15} and lithium chloride (entry 11, Table 1). Then, the 17a−k compounds were treated with O-benzyl hydroxylamine hydrochloride, generating the corresponding O-benzyl oxime ethers 8 and 18a−j, as a mixture of geometric isomers.

Subsequently, the oxime ethers with brominated aromatic rings 18a−b (entries 1−3, Table 2) were subjected to radical conditions under inert atmosphere, with Bu\textsubscript{3}SnH/2,2′-azobisisobutyronitrile (AIBN) (Method A) in cyclohexane at reflux between 6 and 8 h. The reaction proceeded affording the spirocycles 19a (66%) and 19b (64%) as a pair of diastereomers, which were isolated by column chromatography.

In contrast, for the precursor 18c bearing the double bond with two methyl groups (electron-releasing nature) (entry 3, Table 2), the reduction of the intermediate alkoxyaminyl radical predominated affording the monocyclized product 23c (50%) (Scheme 4), with respect to the spiroane compound 19c (11%). This percentage was estimated by nuclear magnetic resonance (NMR) of the crude sample because it was not possible to carry out an effective separation of the expected product. Such behavior demonstrates one more time the nucleophilic nature of such radicals,\textsuperscript{9} and then attempting to increase the yield of the desired compound 19c, MgBr\textsubscript{2}·Et\textsubscript{2}O was used in order to reverse the polarity of the alkoxyaminyl radical and confer it electrophilicity via a complexation reaction with the electron lone pair of the nitrogen atom.\textsuperscript{5} Nevertheless, the reaction did not proceed.

On the other hand, oxime ethers 8 and 18d,e containing an iodinated aromatic ring were reacted via radicals in cyclohexane, using AIBN at reflux (Method A) and BEt\textsubscript{3} at room temperature (Method B), with reaction times decreased to 3 h and similar yields in both methods to afford the expected diastereomeric mixture of spirocyclic products (entries 4, 5, 6, 8, Table 2). In all cases (of the double cyclization by radicals) oxime ethers (10 y 20a−e) E and Z were obtained as minor products (9−28%) due to the premature reduction of the aryl radical with Bu\textsubscript{3}SnH (Table 2). It is remarkable that the diastereoselectivity of this reaction increased when triethylborane (Et\textsubscript{3}B) was used, especially in compound 19a bearing the

| entry | X   | R\textsuperscript{1} | R\textsuperscript{2} | (A) product (%) | trans/cis (%) | (B) product (%) | trans/cis (%) |
|-------|-----|----------------------|----------------------|-----------------|--------------|----------------|--------------|
| 1     | Br  | CO\textsubscript{2}Et | H                    | 19a (66)        | 59/41        | 19a (65)       | 90/10        |
| 2     | Br  | Ph                   | H                    | 19b (64)        | 66/34        | 19b (56)       | 70/30        |
| 3     | Br  | Me                   | Me                   | 19c (11)        | 20a (28)     | 19c (11)       | 20a (9)      |
| 4     | I   | CO\textsubscript{2}Et | H                    | 19a (58)        | 80/20        | 19a (56)       | 80/20        |
| 5     | I   | Ph                   | H                    | 19b (56)        | 63/37        | 19b (56)       | 63/37        |
| 6     | I   | 4-ClC\textsubscript{6}H\textsubscript{4} | H   | 19d (20)       | 100/0        | 19d (23)       | 100/0        |
| 7     | I   | Ph                   | Ph                   | 19e (57)        | 100/0        | 19e (50)       | 100/0        |
| 8     | I   | CN                   | H                    | 9 (66)          | 69/31        | 9 (64)         | 78/22        |

Scheme 4. Feasible Stages for the Domino Radical Bicyclization of the Oxime Ethers 18a−g

Table 2. Domino Radical Bicyclization Reaction of O-Benzyl Oxime Ethers 8 and 18a−e
diastereomers of 19b (Supporting Information). In turn, one of the diastereomers 9 was characterized with the trans configuration by X-ray diffraction.\textsuperscript{11}

The cis and trans diastereomers displayed marked differences in the chemical shift of the CH at the pyrrolidinic ring and the OCH\textsubscript{2}Ph group in the \textsuperscript{1}H NMR spectra. As a general rule, trans diastereomers showed these signals at lower field compared to cis diastereomers. On the other hand, diastereotopic methylene protons of the benzyloxy groups appeared as two doublets, separated by approximately 0.06 and ~0.38 ppm in the trans and cis diastereomers, respectively. As shown in Table 2, the trans spiranes were always observed as the major products.

In addition, the radical bicyclization of precursor 18g showed complete diastereoselectivity for the product, spirocyclic 19e again in trans configuration (entry 7, Table 2), established by the NOESY-1D experiment. Thus, when selective irradiation was applied on H\textsubscript{2} proton, a spatial coupling with the protons of the benzyloxy group was noticeable and by selectively irradiating the hydrogens of that group, other coupling was observed with the hydrogens of the cyclopentane (Figure 2 and the Supporting Information).

![Figure 1](image1.png)

**Figure 1.** NOESY-2D couplings of the trans diastereomer 19b (one enantiomer is shown).

![Figure 2](image2.png)

**Figure 2.** NOESY-1D couplings of protons of the trans diastereomer 19e (one enantiomer is shown).

Finally, the spirocycle trans-19d substituted with 4-ClC\textsubscript{6}H\textsubscript{4} group was isolated at the lowest yield, although the \textsuperscript{1}H NMR spectrum of the crude product showed significant presence of the expected compound as a mixture of cis and trans diastereomers. The above suggests a decomposition event during the purification process by chromatography (entry 7, Table 2). With respect to precursor 18h containing the aryl group substituted with a NO\textsubscript{2} at position 4, the domino cyclization reaction did not proceed.

Based on the above results, as well as previous studies,\textsuperscript{7} we reasoned a chain transfer radical for the domino bicyclization reaction, where the halogen atom is abstracted by tributylstannyl radicals from the oxime ethers 8 and 18a–h to afford aryl radicals 21. These last underwent an intramolecular S-exo-trig closure on the imino function to generate alkoxyaminyl radicals 22, which were captured intramolecularly by the double bond of the alkenyl moiety by the azaspiro[4,4]nonane core (Scheme 4). Formation of side products 20 and in one case, the monocyclized product 23c (Table 2), corroborates the mediation of aryl and alkoxyaminyl radicals 21 and 22, respectively, in the domino radical bicyclization process.

As shown in Table 2, the domino radical bicyclization led to diastereomeric mixtures of the spirocyclics 19a, b, e, and 9 with a predominance of the trans-stereoisomer. These results are in agreement with the "Beckwith–Houk ET model,\textsuperscript{16}" which predicts that the major product arises when the substituent occupies an equatorial position in the pseudo-chair conformation for cyclizations S-exo of 2-substituted 5-hexenyl radicals to give predominantly trans-1,3-disubstituted cyclopentanes. Based on this model, in Scheme 5A, equatorial and axial pseudo-chair conformations of alkoxyaminyl radicals 22b allow to observe the preference of chair-equatorial conformation before the second cyclization gives rise to trans diastereomer 19b.

On the other hand, the bicyclization of compound 18g with two phenyl substituents at the end of the olefin part gave rise exclusively to trans stereoisomer 19e. In this case, the pseudo-chair axial conformation is less stable than the pseudo-chair equatorial. Additionally, the steric hindrance between the phenyl groups and the indenic nucleus preclude the second cyclization. See Scheme 5B.

In addition, considering the excellent reactivity of vinyl radicals for addition onto the imine function in oxime ethers,\textsuperscript{17,18} two new precursors 18ij (entries 9–10, Table 1) were designed including an alkenyl moiety, instead of the 2-halophenyl groups. When the radical conditions were applied to these precursors, only spirocyclic products 25ij (Table 3) were obtained without evidence of reduction products. This behavior either suggests that the rate of the first cyclization could be faster in comparison with aryl radicals and/or that the stannylvinylnyl radicals are reduced slower than the aryl radical intermediates.

A hypothetical pathway could be described by the intermolecular addition of tri-n-butylstannyl radicals on the triple bond to afford stannylvinyl radicals 26ij, which are added to the oxime function via a S-exo-trig closure, generating alkoxyaminyl radicals 27ij. These, in turn, are captured by the double bond of the alkenyl moiety in another S-exo-trig closure to obtain stannylated spirocycles, 28ij (Scheme 6).

After removal of cyclohexane, a mixture of silica gel/AcOH/DCM was added to eliminate the tri-n-butylstannyl group (dehydrostannylation), achieving the expected spirocyclic products 25ij (Table 3). The diastereomeric pair configuration for the spirocycles 25i, assigned in the same way as it was done for compounds 19a, b, d, e (differentiation of doublets between methylenic protons of the benzyloxy group: trans = 0.05 ppm and cis = 0.2 ppm).
along with the absence of steric hindrance which makes the addition of the alkoxyaminyl radical to the C=C bond in both conformations difficult (Scheme 7). However, it is worth mentioning that these compounds showed a predominance of the trans stereoisomer when Et$_3$B was used as an initiator (Method B) at room temperature.

Finally, the domino radical bicyclization from oxime ether 18j resulted in a sole product, which was assigned a trans configuration by comparison with the cyclization of the analogous oxime ether 18e \[ \text{Scheme 5B}. \] Unfortunately, it was not possible to differentiate the methylene hydrogens of the cyclopentane and those of the pyrrolidinic nucleus to achieve a selective irradiation of protons in a NOESY experiment. Here, the high diastereoccontrol observed for the stannilated spirocyclic 28j (R$_1$ = R$_2$ = Ph) could be explained as described for 28i (Scheme 7). With 28j the free movement of the n-butyl groups around the tin atom in the transition state would generate steric hindrance with any of the phenyl groups linked to the double bond.

It is noteworthy that this research work, focused on the construction of 1-azaspiro[4.4]nonane derivatives, constitutes the second documented approach toward these target compounds via tandem radical bicyclization with better yields than the pioneering work of Bowman et al.$^5$ Besides, this is the third example in the literature that considers the simultaneous formation of two rings, accounting for both ionic and radical reactions. Another relevant aspect to point out is that the use of Et$_3$B as the radical initiator allowed us to perform the synthesis under mild reaction conditions and improved diastereoselectivity.

**CONCLUSIONS**

In summary, we have successfully developed a synthetic methodology to obtain 1-azaspiro[4.4]nonane derivatives by a domino radical bicyclization involving aryl/stannylvinyl and alkoxyaminyl radicals. The new spirocyclic compounds 19 and 25 were synthesized in moderate yields as a mixture of diastereomers (in most cases) with predominance of the trans configuration starting from O-benzyl oxime ethers containing a brominated or iodinated aromatic ring or terminal alkynyl group and an alkenyl moiety. Two radical initiators were used: AIBN at reflux and Et$_3$B at room temperature. Their comparison shows that the reaction times (3 h) with the Et$_3$B initiator are shorter versus 6 h for reactions with AIBN, while diastereoselectivity increases remarkably.

On the other hand, when aryl radicals were present, domino radical bicyclization displayed side products due to their premature reduction. In contrast, in those compounds exhibiting the terminal alkynyl group and generating stannylvinyl radicals, no side products were observed. Furthermore, O-benzyl oxime ethers with two phenyl groups linked to the alkynyl moiety displayed complete diastereoselectivity in the domino bicyclization process. Last, but not less
important, the obtained compounds with this synthetic methodology are alkoxyamines, which could generate nitroxides (or aminoxyl radicals). Currently, our research group is making efforts to optimize the design and synthesis of other structurally modified alkoxyamines that can be used in nitroxide-mediated radical polymerization.

**EXPERIMENTAL SECTION**

**General Remarks.** Melting points were determined in open capillary tubes on Stuart SMP10. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck); the spots were visualized under UV light (254 nm). Column chromatography and flash column chromatography were conducted under silica gel (Merck, 70–230 or 230–400 mesh). The chemical structures of intermediate and final products were elucidated by nuclear magnetic resonance spectra (1H NMR, 13C NMR) which were recorded on a Mercury 400 and 500 MHz, Gemini 300, VXR 300, and a Bruker AVANCE II 400 MHz spectrometer. Elemental analysis was determined on a Finnigan 4021 with GC coupled Kratos MS-80 with a solution of toluene/hexane (15%) to remove organotin byproducts (monitored by TLC). After removal of cyclohexane, the residue (in both methods) was dissolved in ethyl acetate, and the combined organic extracts dried with anhydrous magnesium sulphate. Finally, the solvent was removed under reduced pressure and the crude product filtered on a short column charged with a silica gel 70–230 mesh and eluted initially with hexane, then with a solution of toluene/hexane (15%) to remove organoinert impurities. After evaporation of the solvent, this crude prepurified was passed over flash column chromatography filled with a silica gel 230–400 mesh or preparative plate to obtain the corresponding spirocyclic compounds and the byproducts.

**Scheme 7. Conformational Equilibrium of the Equatorial and Axial pseudo-chairs for the Alkoxyaminyl Radical, 27i and Their Capture by the Olefinic Appendix**

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trans-5′-Benzyl-1′-(benzoxyl)-2,3-dihydrospiro[indene-1,2′-pyrrolidine] (19b). Method (A). Yellow oil (106.0 mg, 64%). cis diastereomer (36.0 mg, 23%); trans diastereomer (70.7 mg, 41%). Compound 19b was prepared according to the general procedure from oxime ether 18b (156.0 mg, 0.42 mmol), tributyltin hydride (129.0 μL, 0.47 mmol), AIBN (23.0 mg, 0.13 mmol), and cyclohexane (21.0 mL) during 6 h. The crude product was purified by column chromatography, silica gel 60–200 mesh (15–25% DCM, 5% gradient). 1H NMR (CDCl₃, 500 MHz): δ (ppm) 1.97 (m, 1H), 2.70 (dd, 1H, J = 13.0 y 4.0 Hz), 3.31–3.41 (m, 1H), 4.04 (d, 1H, J = 10.2 Hz), 4.43 (d, 1H, J = 10.2 Hz), 6.94–6.98 (m, 2H), 7.20–7.30 (m, 11H), and 7.51–7.54 (m, 1H). 13C NMR (DMSO-d₆, 100 MHz): δ (ppm) 24.2, 29.8, 29.9, 33.5, 40.3, 64.8, 76.7, 77.0, 123.6, 124.2, 125.8, 126.2, 127.5, 127.9, 128.1, 128.4, 128.9, 136.9, 139.3, 144.0, and 145.7. HRMS (ESI-TOF) m/z: [M + Na]⁺ calc for C₂₆H₂₇NONa, 392.1985; found, 392.1976.

O-Benzyl-N-(1-(4-methylpent-3-en-1-yl)-2,3-dihydro-1H-inden-1-yl)hydroxylamine (23c). Method (A). Yellow oil (57.8 mg, 50%). Compound 23c was prepared according to the general procedure from oxime ether 18b (156.0 mg, 0.36 mmol), tributyltin hydride (100.0 μL, 0.37 mmol), AIBN (17.0 mg, 0.10 mmol), and cyclohexane (14.0 mL) during 6 h. The crude product was purified by column chromatography, silica gel 60–200 mesh (15–25% DCM, 5% gradient). 1H NMR (CDCl₃, 300 MHz): δ (ppm) 1.54 (s, 3H), 1.66 (s, 3H), 1.72–1.81 (m, 1H), 1.86–2.05 (m, 3H), 2.08–2.22 (m, 2H), 2.79–2.89 (m, 1H), 2.94–3.04 (m, 1H), 4.56 (d, 2H, J = 11.4 Hz), 4.61 (d, 2H, J = 11.4 Hz), 5.07–5.12 (m, 2H), 5.54 (s, 1H), and 7.15–7.34 (m, 9H). 13C NMR (CDCl₃, 100 MHz): δ (ppm) 17.9, 23.3, 25.9, 30.4, 34.7, 36.8, 72.7, 77.2, 124.5, 124.6, 128.3, 127.8, 129.7, 128.4, 128.5, 131.7, 138.3, 144.4, and 145.5. HRMS (ESI-TOF) m/z: [M + Na]⁺ calc for C₂₆H₂₇NONa, 344.1990; found, 344.1975.

trans-1′(Benzhydryl)-5′-(4-chlorophenylmethyl)-2,3-dihydrospiro[indene-1,2′-pyrrolidine] (19d). Method (A). Yellow oil trans diastereomer (16.8 mg, 20%). Compound 19d was prepared according to the general procedure from oxime ether 18f (124.0 mg, 0.23 mmol), tributyltin hydride (0.08 mL, 0.38 mmol), AIBN (9.6 mg, 0.06 mmol), and cyclohexane (10.6 mL) during 3 h. The crude product was purified by preparative plate chromatography (silica gel, 1000 μm, 10 cm × 20 cm) with two elutions with 5% ethyl acetate/hexane. Method (B). Yellow oil trans diastereomer (26.0 mg, 23%). Compound 19d was prepared according to the general procedure from oxime ether 18f (150.0 mg, 0.23 mmol), tributyltin hydride (0.90 mL, 0.34 mmol), Et₂B (0.70 mL, 0.70 mmol), and cyclohexane (14.0 mL). The crude product was purified by preparative plate chromatography (silica gel, 1000 μm, 10 cm × 20 cm) with two elutions with 5% ethyl acetate/hexane. 1H NMR (CDCl₃, 400 MHz): δ (ppm) 1.59–1.69 (m, 2H), 1.91–2.19 (m, 4H), 2.47 (ddd, 1H, J = 13.2, 7.8, 2.6 Hz), 2.67 (dd, 1H, J = 13.1, 9.2 Hz), 2.84 (ddd, 1H, J = 15.7, 8.6, 2.6 Hz), 3.06–3.18 (m, 2H), 3.60–3.68 (m, 1H), 4.45 (d, 1H, J = 10.8 Hz), 4.51 (d, 1H, J = 10.7 Hz), 7.06 (ddd, 2H, J = 7.0, 2.6, 1.6 Hz), 7.16 (d, 2H, J = 8.1 Hz), and 7.22–7.30 (m, 8H). 13C NMR (CDCl₃, 100 MHz): δ (ppm) 27.0, 30.5, 33.9, 38.7, 40.3, 67.7, 78.8, 124.3, 125.2, 125.9, 127.6, 128.1, 128.3, 130.5, 131.2, 137.4, 138.4, 144.9, and 145.4. HRMS (ESI-TOF) m/z: [M + H⁺] calc for C₂₆H₂₇NOCl, 404.1781; found, 404.1781.

trans-5′-Benzhydryl-1′-(benzoxyl)-2,3-dihydrospiro[indene-1,2′-pyrrolidine] (19e). Yellow oil trans diastereomer (40.6 g, 57%). Method (A). Compound 19e was prepared according to the general procedure from oxime ether 18g (94.0 mg, 0.16 mmol), tributyltin hydride (54.0 μL, 0.20 mmol), AIBN (7.0 mg, 0.04 mmol), and cyclohexane (8.0 mL). The crude product was purified by preparative plate chromatography (silica gel, 1000 μm, 10 cm × 20 cm) with two elutions with 5% diethyl ether/hexane. Method (B). Yellow oil trans diastereomer (53.5 g, 50%). Compound 19e was prepared according to the general procedure from oxime ether 18g (141.0 mg, 0.24 mmol), tributyltin hydride (0.08 mL, 0.29 mmol), Et₂B (0.60 mL, 0.60 mmol), and cyclohexane (12.0 mL). The crude product was purified by preparative plate chromatography (silica gel, 1000 μm, 10 cm × 20 cm) with two elutions with 5% diethyl ether/hexane. 1H NMR (CDCl₃, 400 MHz): δ (ppm) 1.74–1.79 (m, 2H), 1.85–1.92 (m, 2H), 1.98–2.11 (m, 2H), 2.80–2.95 (m, 2H), 3.01–3.08 (m, 1H), 3.74 (s, 2H), 4.12–4.18 (m, 1H), 4.38 (s, 1H), 6.62–6.63 (m, 1H).
Yellow oil (51.2 mg, 64%). Diastereomers: cis 11.2 mg (14%), trans 40.0 mg (50%). Compound 9 was prepared according to the general procedure from oxime ether 8 (112.3 mg, 0.25 mmol), tributylhydride (0.08 mL, 0.28 mmol), AIBN (14 mg, 0.09 mmol), and cyclohexane (13.0 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (60–95% benzene/hexane, 5% gradient). Method (B). Yellow oil (51.2 mg, 64%). Diastereomers: cis 11.2 mg (14%), trans 40.0 mg (50%). Compound 9 was prepared according to the general procedure from oxime ether 8 (112.3 mg, 0.25 mmol), tributylhydride (0.08 mL, 0.28 mmol), AIBN (14 mg, 0.09 mmol), and cyclohexane (13.0 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (60–95% benzene/hexane, 5% gradient).

acetic acid were added, the mixture was stirred for 12 h, filtered, washed with chloroform, and finally concentrated under reduced pressure. Finally, the solvent was removed and the crude product filtered on a short column charged with a silica gel 70–230 mesh and eluted initially with hexane, then with a solution of toluene/hexane (15%) to remove organimpurities. After evaporation of the solvent, this crude prepurified was passed over flash column chromatography filled with a silica gel 230–400 mesh to obtain the corresponding spirocyclic compounds 25.

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2H), and 7.15–7.55 (m, 17H); 13C NMR (CDCl₃, 100 MHz): δ (ppm) 25.7, 30.8, 34.9, 56.3, 67.3, 76.6, 79.0, 124.6, 126.2, 126.4, 127.5, 127.9, 128.2, 128.4, 128.9, 129.0, 137.1, 143.9, 145.0, and 145.8. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₅H₁₄N₂O, 446.2484; found, 446.2484.

trans/cis-2-(1′-Benzoylxy)-2,3-di hydrospiro[indene-1,2′-pyr roolidin]-5′-yl)acetonitrile (9). Method (A). Yellow oil (48.9 mg, 66%). Diastereomers: cis 15.3 mg (21%), trans 33.6 mg (45%). Compound 9 was prepared according to the general procedure from oxime ether 8 (104.5 mg, 0.23 mmol), tributylhydride (0.08 mL, 0.28 mmol), AIBN (14 mg, 0.09 mmol), and cyclohexane (11.5 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (60–95% benzene/hexane, 5% gradient). Method (B). Yellow oil (51.2 mg, 64%). Diastereomers: cis 11.2 mg (14%), trans 40.0 mg (50%). Compound 9 was prepared according to the general procedure from oxime ether 8 (112.3 mg, 0.25 mmol), tributylhydride (0.08 mL, 0.28 mmol), AIBN (14 mg, 0.09 mmol), and cyclohexane (13.0 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (60–95% benzene/hexane, 5% gradient).

Conditions described earlier as Methods (A) and (B) were applied. In chloroform or methanol (0.22 M) were added, the mixture stirred for 12 h, filtered, washed with chloroform, and finally concentrated under reduced pressure. Finally, the solvent was removed and the crude product filtered on a short column charged with a silica gel 70–230 mesh and eluted initially with hexane, then with a solution of toluene/hexane (15%) to remove organoimpurities. After evaporation of the solvent, this crude prepurified was passed over flash column chromatography filled with a silica gel 230–400 mesh to obtain the corresponding spirocyclic compounds 25.

trans/cis-2-Benzyl-1-(benzyloxy)-6-methylene-1-azaspiro[4.4]nonane (25j). Method (A). Yellow oil, only trans diastereomer (52.2 mg, 58%). Compound 25j was prepared according to the general procedure from oxime ether 18j (89.0 mg, 0.22 mmol), tributylhydride (67.0 µL, 0.24 mmol), AIBN (10.0 mg, 0.06 mmol), and cyclohexane (11.0 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (5–15% ethyl acetate/hexanes, 5% gradient). Method (B). Yellow oil trans diastereomer (482.5 mg, 58%). Compound 25j was prepared according to the general procedure from oxime ether 18j (100.0 mg, 0.24 mmol), tributylhydride (81.6 µL, 0.29 mmol), Et₂B (0.60 mL, 0.60 mmol), and cyclohexane (12.0 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (5–15% ethyl acetate/hexanes, 5% gradient). 1H NMR (CDCl₃, 100 MHz): δ (ppm) 1.73–1.95 (m, 3H), 2.11–2.28 (m, 2H), 2.48 (dd, 2H, J = 17.6, 4.0 Hz), 2.70–2.76 (m, 1H), 2.89–2.97 (m, 1H), 3.03–3.11 (m, 1H), 3.31–3.35 (m, 1H), 4.10 (d, 1H, J = 11.0 Hz), 4.32 (d, 1H, J = 11.0 Hz), 7.04–7.05 (m, 2H), 7.27–7.38 (m, 6H), and 7.57–7.59 (m, 1H); 13C NMR (CDCl₃, 100 MHz): δ carbons (ppm) 22.6, 24.6, 30.2, 30.5, 34.4, 59.9, 77.5, 77.9, 118.1, 124.1, 124.6, 126.6, 128.0, 128.1, 128.2, 129.0, 137.4, 144.5, and 145.1. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₂₅H₂₆N₂O, 391.1810; found, 391.1813.

General Procedure for the Synthesis of Spirocyclic 25. Conditions described earlier as Methods (A) and (B) were also used for this case. But after removal of cyclohexane, dehydrostannylated was carried out; ~14 mL of dichloromethane, ~2.5 g of silica gel 70–230 mesh, and ~5 drops of acetic acid were added, the mixture was stirred for 12 h, filtered, washed with chloroform, and finally concentrated under reduced pressure. Finally, the solvent was removed and the crude product filtered on a short column charged with a silica gel 70–230 mesh and eluted initially with hexane, then with a solution of toluene/hexane (15%) to remove organoimpurities. After evaporation of the solvent, this crude prepurified was passed over flash column chromatography filled with a silica gel 230–400 mesh to obtain the corresponding spirocyclic compounds 25.

trans/cis-2-Benzyl-1-(benzyloxy)-6-methylene-1-azaspiro[4.4]nonane (25j). Method (A). Yellow oil (62.2 mg, 67%). Diastereomers: cis 29.0 mg (31%), trans 33.2 mg (36%). Compound 25i was prepared according to the general procedure from oxime ether 18i (100.0 mg, 0.30 mmol), tributylhydride (100.0 µL, 0.36 mmol), AIBN (12.6 mg, 0.08 mmol), and cyclohexane (15.0 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (1–3.5% ethyl acetate/hexanes, 0.5% gradient). Method (B) (61.6 mg, 45%). Diastereomers: cis 21.6 mg (15%), trans 40.4 mg (30%). Compound 25i was prepared according to the general procedure from oxime ether 18i (150.0 mg, 0.45 mmol), tributylhydride (150.0 µL, 0.54 mmol), Et₂B (1.1 mL, 1.1 mmol), and cyclohexane (22.5 mL). The crude product was purified by flash column chromatography, silica gel 230–400 mesh (1–3.5% ethyl acetate/hexanes, 0.5% gradient).

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**E/Z-Ethyl 6-((Benzyloxy)imino)-8-(2-bromophenyl)oct-2-enate (18a).** Yellow oil (155 mg, 73%). Compound 18a was prepared according to the general procedure from ketone 17a (161 mg, 0.48 mmol), O-benzylhydroxylamine hydrochloride (102 mg, 0.64 mmol), pyridine (0.11 mL, 1.36 mmol), and methanol anhydrous (2 mL). The crude product was purified by column chromatography silica gel 60–200 mesh (50% methylene chloride/hexane). 1H NMR (CDCl3, 400 MHz) E/Z isomers: δ (ppm) 1.27 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 2.20–2.25 (m, 1H), 2.34–2.51 (m, 11H), 2.89–2.95 (m, 4H), 4.17 (q, 2H, J = 7.2 Hz), 4.18 (q, 2H, J = 7.2 Hz), 5.05 (s, 2H), 5.08 (s, 2H), 5.79 (d, 1H, J = 15.6 Hz), 5.80 (d, 1H, J = 15.6 Hz), 6.87–7.09 (m, 2H), 7.17–7.18 (m, 2H), 7.29–7.36 (m, 14H), 7.49 (d, 1H, J = 7.6 Hz), and 7.51 (d, 1H, J = 7.6 Hz). 13C NMR (CDCl3, 100 MHz): δ (ppm) 14.8, 27.7, 28.8, 29.0, 29.6, 32.6, 33.5, 34.8, 60.7, 75.7, 76.1, 122.4, 128.0, 128.1, 128.3, 128.5, 131.0, 133.3, 133.5, 133.6, 140.9, 147.8, 148.2, 159.0, and 166.8. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C26H26BrNO3Na, 446.0988; found, 446.0973.

**E/Z-(2-Bromophenyl)-7-phenylhept-6-en-3-one O-Benzyl Oxime (18b).** Yellow oil (441 mg, 67%). Compound 18b was prepared according to the general procedure from ketone 17b (500 mg, 1.46 mmol), O-benzylhydroxylamine hydrochloride (481 mg, 1.90 mmol), pyridine (0.3 mL, 3.86 mmol), and methanol anhydrous (6 mL). The crude product was purified by column chromatography, silica gel 60–200 mesh (30% methylene chloride/hexanes). 1H NMR (CDCl3, 400 MHz) E/Z isomers: δ (ppm) 2.26–2.65 (m, 12H), 2.92–2.98 (m, 4H), 5.09 (s, 2H), 5.10 (s, 2H), 6.11–6.21 (m, 2H), 6.32–6.40 (m, 2H), 7.00–7.36 (m, 26H), and 7.50 (d, 2H, J = 7.2 Hz). 13C NMR (CDCl3, 100 MHz): δ (ppm) 28.7, 29.1, 29.4, 29.8, 32.3, 33.2, 34.6, 34.6, 75.7, 75.7, 124.4, 124.5, 126.2, 127.2, 127.7, 127.7, 127.8, 128.0, 128.1, 128.2, 128.5, 128.6, 129.5, 129.6, 130.6, 130.7, 132.9, 137.6, 137.7, 138.5, 140.7, 140.8, and 159.7. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C26H26BrNO3Na, 470.1090; found, 470.1075.

**E/Z-(2-Bromophenyl)-7-methyl-6-endo-3-one O-Benzyl Oxime (18c).** Yellow oil (407 mg, 75%). Compound 18c was prepared according to the general procedure from ketone 17c (400 mg, 1.63 mmol), O-benzylhydroxylamine hydrochloride (261 mg, 1.63 mmol), pyridine (0.3 mL, 3.86 mmol), and methanol anhydrous (6 mL). The crude product was purified by column chromatography, silica gel 60–200 mesh (20% DCM/hexanes). 1H NMR (CDCl3, 400 MHz) E/Z isomers: δ (ppm) 1.57 (s, 3H), 1.60 (s, 3H), 1.67 (s, 6H), 2.12–2.24 (m, 6H), 2.36–2.41 (m, 2H), 2.44–2.50 (m, 2H), 2.58–2.64 (m, 2H), 2.91–2.98 (m, 4H), 5.03–5.10 (m, 2H), 5.100 (s, 2H), 5.103 (s, 2H), 7.00 (m, 2H), 7.11–7.20 (m, 4H), 7.29–7.38 (m, 10H), and 7.49–7.53 (m, 2H). 13C NMR (CDCl3, 100 MHz): δ (ppm) 17.8, 18.0, 24.6, 25.2, 25.9, 29.0, 32.4, 33.3, 34.8, 34.8, 75.6, 123.4, 123.5, 124.4, 124.5, 127.7, 127.7, 127.9, 128.0, 128.1, 128.2, 128.4, 130.6, 130.7, 132.4, 132.7, 132.9, 138.6, 140.8, 141.0, and 160.4. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C26H26ClINO, 503.0748; found, 503.0746.

**E/Z-1-(2-Iodophenyl)-7-diphenylhept-6-en-3-one O-Benzyl Oxime (18g).** Yellow oil (1309 mg, 71%). Compound 18g was prepared according to the general procedure from ketone 17g (153.0 mg, 0.32 mmol), O-benzylhydroxylamine hydrochloride (77.4 mg, 0.48 mmol), pyridine (0.1 mL, 1.34 mmol), and chloroform (1.5 mL). The crude product was purified by column chromatography, silica gel 70–230 mesh (7–9% diethyl ether/hexane, 2% gradient). 1H NMR (400 MHz, CDCl3): δ (ppm) 1.97 (d, 2H, J = 7.9 Hz), 2.21–2.32 (m, 1H), 2.30–2.38 (m, 6H), 2.75–2.83 (m, 4H), 4.17–4.33 (m, 4H), 5.01 (s, 4H), 5.71–5.73 (m, 2H), 6.77–6.90 (m, 4H), 6.95 (dd, 1H, J1 = 7.6, J2 = 1.6), 7.10–7.17 (m, 2H), 7.20–7.32 (m, 2H), and 7.69–7.73 (m, 2H). 13C NMR (100 MHz, CDCl3): δ (ppm) 14.3, 27.3, 28.4, 28.6, 29.4, 34.7, 34.7, 36.6, 60.2, 60.3, 75.7, 75.7, 100.1, 100.3 (C1), 121.9, 121.0, 127.7, 128.0, 128.1, 128.3, 128.5, 129.6, 138.1, 138.2, 138.5, 143.6, 143.8, 147.5, 147.8, 158.4, 158.6, 166.4, and 166.6. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C26H26INO4Na, 514.0855; found, 514.0854.
and 0.6 mL dichloromethane). The crude product was purified by column chromatography, silica gel 70–230 mesh (10–14% ethyl acetate/hexane, 2% gradient). \(^1\)H NMR (CDCl3, 400 MHz) \(E/Z\) isomers: \(\delta\) (ppm) 2.31 (t, 2H, \(J = 7.3 \text{ Hz}\)), 2.43–2.61 (m, 10H), 2.90–2.95 (m, 4H), 5.06 (d, 1H, \(J = 7.0 \text{ Hz}\)), 5.09 (s, 3H), 6.32–6.44 (m, 4H), 6.86 (t, 2H, \(J = 7.1 \text{ Hz}\)), 7.10–7.21 (m, 4H), 7.28–7.37 (m, 17H), 7.78 (d, 2H, \(J = 7.8 \text{ Hz}\)), and 8.12 (dd, 4H, \(J = 8.8, 3.4 \text{ Hz}\)). \(^{13}\)C NMR (CDCl3, 100 MHz): \(\delta\) (ppm) 28.1, 29.3, 29.4, 29.6, 33.9, 34.8, 36.7, 37.6, 63.5, 75.6, 75.6, 100.1, 100.3, 123.9, 126.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 129.5, 129.6, 134.7, 134.9, 138.2, 138.3, 143.7, 143.8, 144.0, 144.1, and 158.8. HRMS (ESI-TOF) \(m/z\): [M + Na\(^+\)] calcd for \(C_{26}H_{25}IN_2O\), 563.0808; found, 563.0811.

\(E/Z\)-1-(2-Iodomethyl)-7-(4-nitrophenyl)hept-6-ene-3-one \(O\)-Benzyloxime \((18h)\). Yellow oil (128 mg, 65%). Compound \(18h\) was prepared according to the general procedure from \(O\)-benzyloxime \((159.0 \text{ mg}, 0.37 \text{ mmol})\), O-benzylhydroxylamine hydrochloride (100.0 mg, 0.63 mmol), pyridine (0.07 mL, 0.92 mmol), and mixture of DCM and methanol (1 mL methanol and 0.6 mL dichloromethane). The crude product was purified by column chromatography, silica gel 70–230 mesh (10–14% ethyl acetate/hexane, 2% gradient). \(^1\)H NMR (CDCl3, 400 MHz) \(E/Z\) isomers: \(\delta\) (ppm) 2.31 (t, 2H, \(J = 7.3 \text{ Hz}\)), 2.43–2.61 (m, 10H), 2.90–2.95 (m, 4H), 5.06 (d, 1H, \(J = 7.0 \text{ Hz}\)), 5.09 (s, 3H), 6.32–6.44 (m, 4H), 6.86 (t, 2H, \(J = 7.1 \text{ Hz}\)), 7.10–7.21 (m, 4H), 7.28–7.37 (m, 17H), 7.78 (d, 2H, \(J = 7.8 \text{ Hz}\)), and 8.12 (dd, 4H, \(J = 8.8, 3.4 \text{ Hz}\)). \(^{13}\)C NMR (CDCl3, 100 MHz): \(\delta\) (ppm) 28.1, 29.3, 29.4, 29.6, 33.9, 34.8, 36.7, 37.6, 63.5, 75.6, 75.6, 100.1, 100.3, 123.9, 126.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 129.5, 129.6, 134.7, 134.9, 138.2, 138.3, 143.7, 143.8, 144.0, 144.1, and 158.8. HRMS (ESI-TOF) \(m/z\): [M + Na\(^+\)] calcd for \(C_{26}H_{25}IN_2O\), 563.0808; found, 563.0811.

General Procedure for Synthesis of Ketones 17a–k. Methodology A. A microwave tube was charged with \(\beta\)-ketoester \(16d\)–j (1.00 mmol), LiCl (4.00 mmol), silica gel (70–230 mesh, Merck, 0.40 g per 1.00 mmol of substrate), DMF (25–75 \(\mu\)L), and DCM (3 mL). The mixture was homogenized by stirring and the excess of DCM removed under vacuum. The tube was sealed with its plastic cup and heated in a CEM Discover Microwave reactor (using the dynamic method) until the substrate was consumed (monitored by TLC). The silica gel-supported reaction mixture was cooled to room temperature and poured into a chromatographic column partially filled with silica gel. Then, the product was isolated using a gradient of ethyl ether or ethyl acetate or dichloromethane/hexane mixture.

Methodology B. To a solution of compounds \(\beta\)-ketoester \(16a\)–c (1.00 equiv) in DMSO (1.2 M) were added LiCl (2.00 equiv) and \(H_2O\) (1.00 equiv). The reaction mixture was quenched with brine and extracted with ethyl acetate; the organic layer was dried over \(MgSO_4\). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel.

Methodology C. A microwave tube was charged with \(\beta\)-ketoester \(16k\) (1.00 equiv), LiCl (4.40 equiv), \(H_2O\) (1.5 equiv), and DMF (0.98 M). The tube was sealed with its plastic cup and heated with stirring in a CEM Discover Microwave reactor (using the dynamic method) until the substrate was consumed (monitored by TLC). The mixture was washed with water and extracted with diethyl ether; the organic layer was dried over \(Na_2SO_4\). The solvent was removed, and the product was isolated using gradient of ethyl acetate/hexane mixture.

**Ethyl (E)-8-(2-Bromomethyl)-6-oxooct-2-enoate \((17a)\).** Yellow oil, (171.1 mg, 82%). Compound \(17a\) was prepared according to the general procedure for Methodology B from ethyl \((E)-2-(2-bromomethyl)-3-oxo-7-phenylhept-6-enoate \((16a)\) (440 mg, 1.10 mmol), LiCl (94 mg, 2.20 mmol), and \(H_2O\) (20 mg, 1.11 mmol) in 3 mL of DMSO. The mixture was refluxed at 110 °C for 5 h. The crude product was purified by column chromatography, silica gel 70–200 mesh (30% DCM/hexane). \(^1\)H NMR (CDCl3, 300 MHz): \(\delta\) (ppm) 1.28 (t, 3H, \(J = 7.2 \text{ Hz}\)), 2.43–2.50 (m, 2H), 2.54–2.59 (m, 2H), 2.75 (t, 2H, \(J = 7.6 \text{ Hz}\)), 3.01 (t, 2H, \(J = 7.6 \text{ Hz}\)), 4.17 (q, 2H, \(J = 7.2 \text{ Hz}\)), 5.80 (d, 1H, \(J = 15.2 \text{ Hz}\)), 6.90 (dt, 1H, \(J = 15.6, 6.4 \text{ Hz}\)), 7.03–7.09 (m, 1H), 7.21–7.23 (m, 2H), and 7.51 (d, 1H, \(J = 7.6 \text{ Hz}\)).
1-(2-Bromobenzyl)-7-phenylhept-6-enoic acid (17b). Yellow oil, (500.0 mg, 65%). Compound 17b was prepared according to the procedure for Methodology B from methyl (E)-2-(2-bromobenzyl)-3-oxo-oct-7-en-6-enoate (16b) (940 mg, 2.23 mmol), LiCl (189 mg, 4.46 mmol), and H2O (40 mg, 2.23 mmol) in 5.5 mL of DMF. The mixture was refluxed at 100 °C for 1 h. The crude product was purified by column chromatography, silica gel 60–200 mesh (30% DCM/hexane). 1H NMR (CDCl3, 300 MHz): δ (ppm) 2.36–2.44 (m, 2H), 2.48–2.53 (m, 2H), 2.69 (t, 2H, J = 7.6 Hz), 2.94 (t, 2H, J = 7.6 Hz), 6.08 (dt, 1H, J = 16.0, 6.4 Hz), 6.31 (d, 1H, J = 16.0 Hz), 6.84–7.00 (m, 1H), 7.09–7.25 (m, 7H), and 7.43 (d, 1H, J = 7.8 Hz). 13C NMR (CDCl3, 75 MHz): δ (ppm) 27.4, 30.5, 42.6, 42.8, 124.4, 126.2, 127.8, 128.1, 128.7, 128.9, 130.8, 131.0, 133.0, 137.5, 140.5, and 208.9. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C16H18BrO3Na, 361.0410; found, 361.0418.

(E)-1-(2-Bromophenyl)-7-phenylhept-6-en-3-one (17c). Yellow oil, (822.2 mg, 66%). Compound 17c was prepared according to the procedure for Methodology B from methyl (2-(2-bromobenzyl)-7-methyl-3-oxo-oct-6-enoate (16c) (1500 mg, 4.25 mmol), LiCl (360 mg, 8.50 mmol), and H2O (76 mg, 4.25 mmol) in 11 mL of DMF. The mixture was refluxed at 170 °C for 1 h. The crude product was purified by column chromatography, silica gel 60–200 mesh (30% DCM/hexane). 1H NMR (CDCl3, 300 MHz): δ (ppm) 1.66 (s, 3H), 1.67 (s, 3H), 2.25 (m, 2H), 2.42 (t, 2H, J = 7.1 Hz), 2.73 (t, 2H, J = 7.6 Hz), 3.00 (t, 2H, J = 7.6 Hz), 5.04 (t, 1H, J = 7.2 Hz), 7.02–7.08 (m, 1H), 7.21–7.26 (m, 2H), 7.21–7.26 (m, 2H), and 7.51 (d, 1H, J = 7.8 Hz). 13C NMR (CDCl3, 75 MHz): δ (ppm) 17.9, 22.8, 25.9, 30.6, 42.7, 43.1, 122.9, 124.5, 127.8, 128.1, 130.9, 133.1, 140.6, and 209.7. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C16H16BrO3Na, 365.0511; found, 365.0504.

(E)-1-(2-Bromophenyl)-7-phenylhept-6-enoic acid (17d). Yellow oil, (38 mg, 50%). Compound 17d was prepared according to the procedure for Methodology A from 1-ethyl-8-(2-bromophenyl)-6-oxo-oct-6-enoic acid (16d) (75 mg, 0.17 mmol), LiCl (32 mg, 0.74 mmol), silica gel (68 mg), and DMF (25 mL). The vial was sealed and heated at 120 °C, 200 W for 10 min. The crude product was purified by column chromatography, silica gel 70–230 mesh (11–14% ethyl acetate/hexane). 1H NMR (CDCl3, 400 MHz): δ (ppm) 1.31 (t, 3H, J = 7.2 Hz), 2.47–2.63 (m, 3H), 2.72–2.78 (m, 2H), 2.86–3.21 (m, 3H), 4.21 (q, 2H, J = 2.0 Hz), 5.85 (d, 1H, J = 18.6 Hz), 6.84–6.98 (m, 2H), 7.24–7.31 (m, 2H), and 7.84 (d, 1H, J = 7.0 Hz). Other spectroscopic data were previously reported in the literature.

(E)-1-(2-Iodobenzyl)-7-phenylhept-6-enoic acid (17e). Yellow oil, (822.2 mg, 66%). Compound 17e was prepared according to the procedure for Methodology A from methyl (E)-2-(2-iodobenzyl)-3-oxo-oct-7-en-6-enoate (16e) (900 mg, 1.96 mmol), LiCl (350 mg, 8.04 mmol), silica gel (780 mg), and DMF (50 mL). The vial was sealed and heated at 135 °C, 200 W for 8 min. The crude product was purified by column chromatography, silica gel 70–230 mesh (12–14% ethyl acetate/hexane, 1% gradient). 1H NMR (CDCl3, 400 MHz): δ (ppm) 2.39–2.44 (m, 2H), 2.50–2.53 (m, 2H), 2.65–2.69 (m, 2H), 2.91–2.95 (m, 2H), 6.06–6.14 (m, 1H), 6.32 (d, 1H, J = 15.8 Hz), 6.78–6.82 (m, 1H), 7.05–7.25 (m, 1H), and 7.70–7.76 (m, 1H). Other spectroscopic data were previously reported in the literature.
column chromatography, silica gel 70–230 mesh (6–10% ethyl acetate/hexane, 1% gradient). H NMR (CDCl₃, 400 MHz): δ (ppm) 1.63–1.73 (m, 2H), 1.84 (t, 2H, J = 2.6 Hz), 1.97 (s, 1H), 2.13 (td, 2H, J₁ = 6.8 Hz, J₂ = 2.7 Hz), 2.43–2.47 (m, 2H), 2.54–2.59 (m, 4H), 5.95 (t, 1H, J = 7.4 Hz), and 7.20–7.43 (m, 10H). 13C NMR (CDCl₃, 100 MHz): δ (ppm) 17.8, 22.2, 24.2, 41.1, 42.9, 69.1, 83.6, 127.1, 127.1, 127.3, 127.7, 128.1, 128.3, 139.8, 142.4, 142.8, and 209.5. HRMS (ESI-TOF) m/z: [M + K]+ calcd for C₁₄H₁₄INONa, 341.1308; found, 341.1310.

8-(2-Iodophenyl)-8-oxo-octan-2-ene (17k). Yellow oil, E/Z isomers (35 mg, 47%). Compound 17k was prepared according to the procedure for Methodology A from methyl 7-cyanocinnamaldehyde (17b) (87 mg, 0.22 mmol), LiCl (37 mg, 0.88 mmol), and H₂O₂ (10 mg, 0.54 mmol) in 2 mL of DMF. The vial was sealed and heated at 135 °C, 205 W for 50 s. The crude product was purified by column chromatography, silica gel 70–230 mesh (18% ethyl acetate/hexane, 2% gradient). 1H NMR (CDCl₃, 400 MHz), E/Z isomers: δ (ppm) 2.49–2.80 (m, 12H), 3.01 (t, 4H, J = 8.0 Hz), 5.34 (d, 2H, J = 14.0, 12.0 Hz), 6.51 (dt, 1H, J₁ = 11.0, 8.0 Hz), 6.67 (dt, 1H, J = 16.0, 7.0 Hz), 6.91 (t, 2H, J = 8.0 Hz), 7.21–7.30 (m, 4H), and 7.82 (d, 2H, J = 8.0 Hz). 13C NMR (CDCl₃, 100 MHz): δ (ppm) 25.7, 25.9, 34.7, 40.2, 40.7, 42.6, 42.7, 100.1, 104.4, 100.9, 117.1, 128.2, 128.5, 129.7, 139.6, 143.1, 153.2, 153.9, 206.9, and 207.1. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for C₁₃H₁₂INONa, 362.0018; found, 362.0017.

General Procedure for Synthesis of β-Ketoesters 16a–k. To a suspension of potassium tert-butoxide or sodium hydride (1.00 equiv) in anhydrous THF (~0.33 M) under argon atmosphere, the corresponding β-ketoester (1.00 equiv) was added dropwise. The reaction mixture was stirred for 10 min, and alkyl bromide (1.00–1.05 equiv) was added slowly. The stirring continued for 12 h at room temperature, with monitoring by TLC. Then, the reaction mixture was quenched with water, extracted with ethyl acetate, the organic layer dried over MgSO₄ or Na₂SO₄ and filtered. Finally, the solvent removed and the product was isolated by column chromatography.

1-Ethyl 8-Methyl (E)-7-(2-Bromobenzyl)-6-oxo-octan-2-enedioate (16e). Yellow oil, (1140 mg, 57%). Compound 16e was prepared according to the general procedure from (E)-ethyl 3-oxo-7-phenyl-6-heptenoate (12) (1400 mg, 416 mmol), potassium tert-butoxide (500 mg, 4.37 mmol), ethyl 4-bromo-2-butoxide (1180 mg, 4.58 mmol), and THF (13 mL). The crude product was purified by column chromatography, silica gel 230–400 mesh (30% DCM/hexane). 1H NMR (CDCl₃, 400 MHz): δ (ppm) 1.30 (t, 3H, J = 7.2 Hz), 2.74–2.87 (m, 3H), 2.94–3.07 (m, 3H), 3.64 (t, 1H, J = 7.3 Hz), 3.72 (s, 3H), 4.20 (q, 2H, J = 7.0 Hz), 5.88 (d, 1H, J = 15.6 Hz), 6.80–6.88 (m, 1H), 6.90–6.94 (m, 1H), 7.23–7.31 (m, 2H), and 7.83 (d, 1H, J = 7.8 Hz). 13C NMR (CDCl₃, 75 MHz): δ (ppm) 14.2, 26.9, 34.5, 42.6, 58.2, 61.7, 124.6, 126.1, 126.2, 128.6, 128.7, 131.1, 131.9, 133.0, 137.4, 137.5, 168.8, and 203.8. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₁₄H₁₃BrO₄N, 353.0771; found, 353.0770.

Ethyl (E)-2-(2-Bromobenzyl)-3-oxo-7-phenylhept-6-enioate (16f). Yellow oil, (2470 mg, 77%). Compound 16f was prepared according to the general procedure from (E)-3-oxo-7-phenyl-6-heptenoate (12) (1680 mg, 7.16 mmol), potassium tert-butoxide (870 mg, 7.59 mmol), methyl 4-bromo-2-butoxide (2120 mg, 7.88 mmol), and THF (22 mL). The crude product was purified by column chromatography, silica gel 70–230 mesh (30% DCM/hexane). 1H NMR (CDCl₃, 400 MHz): δ (ppm) 2.47 (q, 2H, J = 6.9 Hz), 2.56–
Methyl (E)-7-(4-Chlorophenyl)-2-(2-iodobenzyl)-3-oxohept-6-enoate (16f). Yellow oil, (460 mg, 52%). Compound 16f was prepared according to the general procedure from methyl 5-(2-iodophenyl)-3-oxopentanoate (14) (618 mg, 1.94 mmol), sodium hydride (80 mg, 1.94 mmol), (E)-1-chloro-4-(3-chloroprop-1-en-1-yl)benzene (370 mg, 1.94 mmol), and THF (3.7 mL). The mixture was refluxed for 18 h, the product was purified by column chromatography, silica gel 70–230 mesh (10–16% ethyl acetate/hexane, 2% gradient). 1H NMR (CDCl3, 400 MHz): δ (ppm) 2.38 (q, 2H, J = 7.4 Hz), 3.74 (s, 3H), 6.14 (dt, 1H, J = 6.6, 6.4 Hz), 3.02–3.07 (m, 2H), 3.67 (t, 1H, J = 7.3 Hz), 3.74 (s, 3H), 6.11 (dt, 1H, J = 7.4, 7.2 Hz), 6.43 (d, 1H, J = 15.8 Hz), 6.90–6.94 (m, 1H), 7.24–7.31 (m, 6H), and 7.83 (d, 1H, J = 8.0 Hz). Other spectroscopic data were previously reported in the literature.14

Yellow oil, (230 mg, 58%). Compound 16g was prepared according to the general procedure from methyl 5-(2-iodophenyl)-3-oxopentanoate (14) (230 mg, 0.80 mmol), potassium tert-butoxide (91 mg, 0.85 mmol), and THF (2.1 mL). The crude product was purified by column chromatography, silica gel 230–400 mesh (10–13% ethyl acetate/hexane, 1% gradient). 1H NMR (CDCl3, 400 MHz): δ (ppm) 2.34 (q, 2H, J = 7.3 Hz), 2.49–2.57 (m, 1H), 2.70–2.78 (m, 1H), 3.27–3.29 (m, 2H), 3.69 (s, 3H), 4.02 (t, 1H, J = 7.5 Hz), 5.98 (t, 1H, J = 7.4 Hz), and 7.16–7.42 (m, 14H).

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Other spectroscopic data were previously reported in the literature.\textsuperscript{22} Yellow oil, (1680 mg, 75%). Compound 12 was prepared according to the general procedure from methyl acetoacetate (1580 mg, 13.5 mmol), sodium hydride (340 mg, 13.5 mmol), n-butyl lithium (5.4 mL, 13.5 mmol) and (E)-(3-bromoprop-1-en-1-yl)-benzene (2000 mg, 9.64 mmol), and THF (36.5 mL). The product was purified by column chromatography, silica gel 70−230 mesh (12−15% ethyl acetate/hexane, 1% gradient).\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ (ppm) 2.50 (dd, 2H, J = 6.8, 7.3, 7.0 Hz), 2.72 (t, 2H, J = 8.0 Hz), 3.46 (s, 2H), 3.72 (s, 3H), 6.17 (dt, 1H, J = 16.0, 7.0 Hz), 6.41 (d, 1H, J = 16.0 Hz), 7.17−7.21 (m, 1H), and 7.26−7.33 (m, 5H). Other spectroscopic data were previously reported in the literature.\textsuperscript{21}

Yellow oil, (1680 mg, 75%). Compound 13 was prepared according to the general procedure from methyl acetoacetate (2152 mg, 18.3 mmol), sodium hydride (880 mg, 22.0 mmol), n-butyl lithium (8.8 mL, 21.2 mmol) and 1-bromo-3-methylbut-2-ene (3612 mg, 24.2 mmol), and THF (12 mL). The product was purified by column chromatography, silica gel 70−230 mesh (5−10% ethyl acetate/hexane, 1% gradient). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ (ppm) 1.61 (s, 3H), 1.68 (s, 3H), 2.22−2.31 (m, 2H), 2.56 (t, 2H, J = 7.2 Hz), 3.45 (s, 2H), 3.73 (s, 3H), and 5.06 (t, 1H, J = 7.2 Hz). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): δ (ppm) 18.0, 22.6, 26.0, 43.4, 49.5, 52.4, 127.1, 133.4, 168.0, and 202.7. HRMS (ESI) calcd for C\textsubscript{10}H\textsubscript{16}NO\textsubscript{3} [(M + Na\textsuperscript{+}), 21113, found, 21099].

Yellow oil, (1680 mg, 75%). Compound 14 was prepared according to the general procedure from methyl acetoacetate (970 mg, 8.36 mmol), sodium hydride (330 mg, 8.36 mmol), n-butyl lithium (3.3 mL, 8.36 mmol) and 1-(bromomethyl)-2-isobenzofuran (1790 mg, 5.97 mmol), and THF (23 mL). The product was purified by column chromatography, silica gel 70−230 mesh (12−15% ethyl acetate/hexane, 1% gradient). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ (ppm) 2.85 (dd, 2H, J = 8.0 Hz), 3.00 (dd, 2H, J = 8.0 Hz), 3.46 (s, 2H), 3.71 (s, 3H), 6.88 (dd, 1H, J = 7.4 Hz), 7.24 (m, 2H), and 7.79 (dd, 1H, J = 8.0 Hz). Other spectroscopic data were previously reported in the literature.\textsuperscript{22}

Yellow oil, (1680 mg, 75%). Compound 15 was prepared according to the general procedure from methyl acetoacetate (420 mg, 3.60 mmol), sodium hydride (143 mg, 3.60 mmol), n-butyl lithium (1.4 mL, 3.60 mmol) and (3-bromoprop-1-en-1-il)dibenzo (700 mg, 2.60 mmol), and THF (11 mL). The product was purified by column chromatography, silica gel 70−230 mesh (12−15% ethyl acetate/hexane, 1% gradient). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ (ppm) 2.52−2.57 (m, 2H), 2.43−2.48 (m, 2H), 2.68−2.71 (m, 2H), 3.45 (s, 2H), 3.75 (s, 3H), 6.05−6.09 (m, 1H), and 7.19−7.43 (m, 10H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): δ (ppm) 23.9, 43.0, 49.0, 52.4, 127.1, 127.1, 127.2, 128.2, 128.4, 129.8, 139.7, 142.3, 143.1, 167.6, and 201.8. Other spectroscopic data were previously reported in the literature.\textsuperscript{22}
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