Synthesis and Reactions of Benzannulated Spiroaminals: Tetrahydrospirobiquinolines

Joshua Almond-Thynne,‡ Andrew J. P. White,‡ Anastasios Polyzos,§,‡§ Henry S. Rzepa,‡ Philip J. Parsons,† and Anthony G. M. Barrett*,†‡

†Department of Chemistry, Imperial College London, London SW7 2AZ, England
‡CSIRO Manufacturing, Clayton, Victoria 3169, Australia
§School of Chemistry, University of Melbourne, Parkville, Melbourne, Victoria 3010, Australia

ABSTRACT: An efficient two-step synthesis of symmetrical and unsymmetrical tetrahydrospirobiquinolines from o-azidobenzaldehydes is reported. A novel series of tetrahydrospirobiquinolines was prepared by sequential double-aldol condensation with acetone, cyclopentanone, and cyclohexanone to form the corresponding o,o′-diazido-dibenzylidene-acetone, -cyclopentanone, and -cyclohexanone derivatives, respectively, and hydrogenation—spirocyclization. The spirodiamines were further derivatized by electrophilic aromatic bromination, Suzuki coupling, and N-alkylation, all of which proceeded with preservation of the spirocyclic core.

INTRODUCTION

Access to a broad range of structurally diverse nitrogen heterocycles is important in probing and understanding biological functions and may lead to the discovery of new medicines and agricultural chemicals. Fused-ring nitrogen heterocycles are considered privileged scaffolds in both medicinal chemistry and agrochemistry. There is a need to expand the structural classes of amines, especially to those including benzannulated systems,3 in these studies, we demonstrated that spirodiamines have not been reported. Inspired by the ubiquitous biological activity of tetrahydroisoquinoline derivatives, we considered that the tetrahydrospirobiquinoline scaffold may provide access to novel pharmacophores and ligands for metal complexation. Indeed, benzannulated spiroketals, 13, (Figure 3) have been well studied and synthesized most notably by Ding, Wang, and Zhou.22–25

RESULTS AND DISCUSSION

By analogy with benzannulated spiroketals, we envisaged that increasing the rigidity of the diaza scaffold of spirodiamine 6 would displace the spirodiamine 6 to aminoimine 7 equilibrium toward the spirane tautomer. We therefore sought to synthesize a range of tetrahydrospirobiquinolines, 14, from the double-aldol condensation of o-azidobenzaldehydes with ketones to provide the corresponding diazido-dibenzylidene-ketones, followed by reductive cyclization (Figure 3). Initial studies were directed toward the synthesis of tetrahydrospirobiquinoline 14a. o-Azidobenzaldehyde 15a was allowed to react with acetone in the presence of aqueous sodium hydroxide to afford diene 17a (94% yield). Subsequent hydrogenation over palladium on carbon gave tetrahydrospirobiquinoline 14a (Scheme 1), the structure of which was confirmed by two-dimensional NMR spectroscopy and X-ray crystal structure determination.

A two-step reaction was used for the synthesis of a range of tetrahydrospirobiquinolines from the corresponding aromatic aldehydes and acetones,26,27 including extended aromatic systems; electron-rich and electron-poor systems; as well as ortho-, meta-, and para-substituted examples, 14b–g (Table 1). The yields show little deviation, with the exceptions of p-Cl (14g, entry 6), for which some dechlorination was observed, and o-Me (14d, entry 4), for which steric congestion is greater.
Furthermore, cyclopentanone and cyclohexanone can readily replace acetone to produce pentacyclic tetrahydrospirobiquinolines 18 and 19, both as single diastereoisomers, as determined by both $^1$H and $^{13}$C NMR spectroscopy (Scheme 2). These are consistent with the symmetrical trans product for cyclopentanone derivative 18 and desymmetrized cis product 19. These relative stereochemistries were confirmed in both cases by X-ray crystallography after tetrabromination (see Supporting Information).

The origins of these diastereoselectivities were probed using dispersion-corrected density functional theory calculations (B3LYP+D3BJ/Def2-TZVPP/SCRF = ethanol) $^{28}$ of relative free energies ($\Delta \Delta G^{298}$), with the assumption of fast equilibria between amine–imine and spirodiamine. The dipole moments computed for the former class were uniformly higher (3.8–4.9 D) than those for the latter (1.1–1.7 D). The equilibrium free energies did not provide sufficient support for the observed diastereoselectivity. We speculate that the stabilities of the two intermediate ketones are predominant factors in the overall stereochemical control. On the basis of the known preferential formation of cis-2,5-dibenzyl-cyclopentanone and cis-2,6-dibenzyl-cyclohexanone on the palladium-catalyzed hydrogenation of the corresponding 2,5- or 2,6-benzylidene ketones and the facile cis to trans isomerization of the former, equivalent cis to trans isomerization took place prior to spirocyclization with spirane 18 but not with spirane 19. $^{29,30}$ Alternatively, the opposite diastereoisomers do not spirocyclize and exist as amine–imine isomers, which were not isolated chromatographically due to their higher polarities. Attempts were made to isolate these compounds as well as to cyclize...
them upon treatment with a variety of Lewis and Brønsted acids; however, this was unsuccessful. Further investigations into these systems are ongoing in our laboratory.

To expand on the potential number of derivatives accessible by the method, unsymmetrical systems were also studied. Application of the known sequential condensation reaction of acetone with two different o-azido-benzaldehyde derivatives, 20 and 22, hydrogenation, and spirocyclization gave tetrahydrospirobiquinolines 24a and 24b (Scheme 3).

Reaction of tetrahydrospirobiquinoline 14a with varying equivalents of N-bromosuccinimide (NBS) gave brominated products 25 and 26 in 56 and 74% yields, respectively.

Table 1. Substrate Scope *

| Entry | Aldehyde | Product | Yield (%) |
|-------|----------|---------|-----------|
| 1     | ![Image](15b) | ![Image](14b) | 67 |
| 2     | ![Image](15c) | ![Image](14c) | 75 |
| 3     | ![Image](15d) | ![Image](14d) | 53 |
| 4     | ![Image](15e) | ![Image](14e) | 82 |
| 5     | ![Image](15f) | ![Image](14f) | 78 |
| 6     | ![Image](15g) | ![Image](14g) | 34 |
| 7c    | ![Image](15a) | ![Image](14a) | 69 |

*Reaction conditions: (i) o-azido-benzaldehyde derivative 15 (2 mmol), Me₂CO (1 mmol), 2 M NaOH (5 mmol), EtOH, 0–25 °C, 4 h; (ii) 10% Pd/C (10 wt %), H₂ (1 atm), EtOH, 25 °C, 16 h. *Isolated yield over two steps. *Aldehyde, 40 mmol scale.

Scheme 2. Synthesis of Pentacyclic Tetrahydrospirobiquinolines 18 and 19
Dibromination first occurs para to the nitrogen to yield the dibromo analogue 25; then, it occurs ortho to the nitrogen to yield the tetrabromo analogue 26 (Scheme 4), with both structures being confirmed by X-ray crystal structure determinations.

Bromide 26 was converted to tetraphenyl-derivative 27 (67%) by Suzuki–Miyaura coupling with phenylboronic acid (Scheme 5). Most importantly, this demonstrates the robustness of the benzannulated spirodiamine core, which tolerates palladium-mediated cross-coupling. The structure of spirane-diamine 27 was confirmed by X-ray crystal structure determination.

We also investigated derivatization by substitution at the nitrogen of the spirane center. Unsurprisingly, a combination of electronics and steric congestion of the aniline nitrogens mandated forcing conditions for alkylation reactions. Thus, alkylation of tetrahydrospirobiquinoline 14a with n-butyl-lithium in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) and iodomethane gave dimethyl derivative 28a (90%), and allyl bromide afforded the diallyl derivative 28b (81%), again with preservation of the spirocyclic framework.
ACSM Omega

Article

(Scheme 6). This is in contrast to halogenation of spirodiamine 6, which results in the reaction of the amino group of aminooxime tautomer 7 (Figure 2). Diallyl tetrahydrospirobiquinoline 28b smoothly underwent ring-closing metathesis, giving pentacyclic tetrahydrospirobiquinoline 29. The structure of spiran-diamine 29 was confirmed by X-ray crystal structure determination.

■ CONCLUSIONS

We have developed a chemically robust and straightforward procedure for the synthesis of tetrahydrospirobiquinoline derivatives, a class of understudied heterocyclic compounds. Further syntheses and applications of spirodiamines, including tetrahydrospirobiquinolines, will be reported in due course.

■ EXPERIMENTAL SECTION

General Remarks. All reactions were carried out in oven-dried glassware under atmospheric conditions using commercially supplied solvents and reagents, unless otherwise stated. Large-scale hydrogations were carried out in a Parr hydrogenator. Column chromatography was carried out on silica gel (254 aluminum plates, with visualization under UV light or by staining with an acidic vanillin dip). Melting points otherwise stated (eluents are given in parentheses). Analytical microanalysis, calcd for C_{11}H_{15}N_{2}O: C, 67.00; H, 3.58; N, 21.31; found: C, 66.78; H, 3.39; N, 21.12.

8-Azidoquinolone-7-carbaldehyde (15c). NaN_{3} (1.78 g, 27.4 mmol, 3.0 equiv) was added to 8-nitroquinolone-7-carbaldehyde (1.85 g, 9.13 mmol, 1.0 equiv) in anhydrous DMF (14 mL) and Et_{3}N (260 μL, 1.82 mmol, 0.2 equiv) under an argon atmosphere and heated at 60 °C with sparging with argon. After 1 h, the mixture was allowed to cool, diluted with H_{2}O (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed sequentially with 5% aqueous LiCl (3 × 50 mL) and brine (1 × 50 mL) and dried (MgSO_{4}). After rotary evaporation, the residue was chromatographed (gradient; pentane/CH_{2}Cl_{2} 1:1 to 0:1) to give azide 15c (785 mg, 43%) as a yellow solid: mp 125–126 °C (CH_{2}Cl_{2}); IR ν = 2125, 1675, 1384, 1295, 1256, 837 cm\(^{-1}\); \(^{1}H\) NMR (400 MHz, CDCl_{3}) δ 10.68 (s, 1H), 8.95 (d, J = 4.0 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 6.73–7.50 (m, 2H); \(^{13}C\) NMR (101 MHz, CDCl_{3}) δ 189.3, 148.9, 143.5, 141.8, 136.6, 132.4, 125.7, 124.1, 123.8, 123.7; HRMS (ES+), calcd for C_{20}H_{15}N_{3}O (M + H\(^{+}\)): 319.0966; found: 319.0821; microanalysis, calcd for C_{20}H_{15}N_{3}O: C, 80.03; H, 5.39; N, 29.80.

8-Azido-1-phenyl-1H-1,2,2′-spirobiquinoline (14a) (Scheme 6). This involves the reaction of 1-phenyl-1H-2,2′-spirobiquinoline 14a (185 mg, 74%) as a colorless crystalline solid. A sample was chromatographed (pentane/CH_{2}Cl_{2} 1:1): mp 131–132 °C (CH_{2}Cl_{2}); IR ν = 3372, 3047, 2915, 1600, 1488, 1468, 743 cm\(^{-1}\); \(^{1}H\) NMR (400 MHz, CDCl_{3}) δ 7.11–6.96 (m, 4H), 6.70 (td, J = 7.4, 1.2 Hz, 2H), 6.48 (dd, J = 7.9, 1.2 Hz, 2H), 4.27 (s, 2H), 2.91 (t, J = 6.8 Hz, 4H), 2.10–1.90 (m, 4H); \(^{13}C\) NMR (101 MHz, CDCl_{3}) δ 142.6 (2C), 129.2 (2C), 127.4 (2C), 120.2 (2C), 117.8 (2C), 114.8 (2C), 63.5, 33.3 (2C), 23.4 (2C); HRMS (ESI), calcd for C_{16}H_{19}N_{5}O (M + H\(^{+}\)): 291.1542; found: 291.1546; microanalysis, calcd for C_{16}H_{19}N_{5}O: C, 78.12; H, 5.78; N, 12.11; found: C, 78.24; H, 5.40; N, 12.08.

8-Azido-1-(2-fluorophenyl)-1H-1,2,2′-spirobiquinoline (14b) (Scheme 6). This involves the reaction of 1-(2-fluorophenyl)-1H-2,2′-spirobiquinoline 14a (235 mg, 185 mg, 21% yield) as a white amorphous solid (235 mg, 74%) as a colorless crystalline solid. A sample was chromatographed (pentane/CH_{2}Cl_{2} 1:1): mp 131–132 °C (CH_{2}Cl_{2}); IR ν = 3372, 3047, 2915, 1600, 1488, 1468, 743 cm\(^{-1}\); \(^{1}H\) NMR (400 MHz, CDCl_{3}) δ 7.11–6.96 (m, 4H), 6.70 (td, J = 7.4, 1.2 Hz, 2H), 6.48 (dd, J = 7.9, 1.2 Hz, 2H), 4.27 (s, 2H), 2.91 (t, J = 6.8 Hz, 4H), 2.10–1.90 (m, 4H); \(^{13}C\) NMR (101 MHz, CDCl_{3}) δ 142.6 (2C), 129.2 (2C), 127.4 (2C), 120.2 (2C), 117.8 (2C), 114.8 (2C), 63.5, 33.3 (2C), 23.4 (2C); HRMS (ESI), calcd for C_{16}H_{19}N_{5}O (M + H\(^{+}\)): 291.1542; found: 291.1546; microanalysis, calcd for C_{16}H_{19}N_{5}O: C, 78.12; H, 5.78; N, 12.11; found: C, 78.24; H, 5.40; N, 12.08.

8-Azido-1-(2-fluorophenyl)-1H-2,2′-spirobiquinoline (14b) (Scheme 6). This involves the reaction of 1-(2-fluorophenyl)-1H-2,2′-spirobiquinoline 14a (235 mg, 74%) as a colorless crystalline solid. A sample was chromatographed (pentane/CH_{2}Cl_{2} 1:1): mp 131–132 °C (CH_{2}Cl_{2}); IR ν = 3372, 3047, 2915, 1600, 1488, 1468, 743 cm\(^{-1}\); \(^{1}H\) NMR (400 MHz, CDCl_{3}) δ 7.11–6.96 (m, 4H), 6.70 (td, J = 7.4, 1.2 Hz, 2H), 6.48 (dd, J = 7.9, 1.2 Hz, 2H), 4.27 (s, 2H), 2.91 (t, J = 6.8 Hz, 4H), 2.10–1.90 (m, 4H); \(^{13}C\) NMR (101 MHz, CDCl_{3}) δ 142.6 (2C), 129.2 (2C), 127.4 (2C), 120.2 (2C), 117.8 (2C), 114.8 (2C), 63.5, 33.3 (2C), 23.4 (2C); HRMS (ESI), calcd for C_{16}H_{19}N_{5}O (M + H\(^{+}\)): 291.1542; found: 291.1546; microanalysis, calcd for C_{16}H_{19}N_{5}O: C, 78.12; H, 5.78; N, 12.11; found: C, 78.24; H, 5.40; N, 12.08.

DOI: 10.1021/acsomega.7b00482

ACS Omega 2017, 2, 3241–3249
3,3',4,4'-Tetrahydro-1H,1'H-2,2'-spirobi[1,10]-phenanthroline (14c). 8-Azaquinoline-7-carbaldehyde (15c) gave spirobiquinoline 14c (264 mg, 75%) as a yellow solid. A sample was chromatographed (gradient; CHCl3/MeOH 1:0 to 9:1); mp 153–155 °C (CHCl3); IR ν = 3402, 3040, 2830, 1508, 1472, 1325, 819, 793 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.86 (dd, J = 4.2, 1.7 Hz, 2H), 8.05 (dd, J = 8.2, 1.7 Hz, 2H), 7.33–7.28 (m, 4H), 7.10 (d, J = 8.2 Hz, 2H), 6.55 (s, 2H), 3.23 (dd, J = 17.3, 9.1, 5.7 Hz, 2H), 3.11 (dt, J = 17.1, 6.0 Hz, 2H), 2.37–2.27 (m, 2H), 2.16 (dd, J = 12.7, 9.1, 5.7 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 147.3 (2C), 138.7 (2C), 137.6 (2C), 135.9 (2C), 128.7 (2C), 127.6 (2C), 120.8 (2C), 116.0 (2C), 114.2 (2C), 60.3, 33.3 (2C), 24.0 (2C); HRMS (ESI), calcd for C₁₉H₂₃N₂O₂ (M + H⁺): 311.1760; found: 311.1759.

The sample was chromatographed (pentane/CH₂Cl₂ 1:1) to give unsymmetrical aza-dibenzo[3,3′]-carbazole (15d); mp 115 mg, 42% as a white solid. A sample was chromatographed (pentane/CHCl₃ 1:1); mp 109–111 °C (pentane); IR ν = 3384, 2918, 1605, 1474, 1261, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13–7.00 (m, 5H), 6.71 (td, J = 7.4, 1.2 Hz, 2H), 6.50 (dd, J = 7.8, 1.1 Hz, 2H), 4.12 (2H, 2H), 2.90 (dd, J = 15.9, 5.7 Hz, 2H), 2.65 (dd, J = 15.9, 5.7 Hz, 2H), 2.20 (td, J = 7.3, 5.5 Hz, 2H), 2.01–1.88 (m, 2H), 1.51–1.38 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 142.7 (2C), 128.9 (2C), 127.1 (2C), 121.3 (2C), 117.7 (2C), 75.3, 113.6 (2C), 43.8 (3C), 30.1 (2C), 27.78 (2C); HRMS (ESI), calcd for C₂₃H₃₄N₄Cl (M + H⁺): 355.1772; found: 355.1772.

The sample was chromatographed (pentane/CHCl₃ 1:1); mp 84–85 °C (CHCl₃); IR ν = 3113, 2956, 1508, 1472, 1325, 819, 793 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, J = 8.3, 2.5 Hz, 2H), 6.04 (d, J = 2.4 Hz, 2H), 4.27 (s, 2H), 3.73 (s, 6H), 2.83 (t, J = 6.7 Hz, 4H), 1.94 (tt, J = 12.8, 5.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2 (2C), 143.5 (2C), 130.0 (2C), 112.7 (2C), 104.0 (2C), 99.9 (2C), 63.3, 55.32 (2C), 33.5 (2C), 22.6 (2C); HRMS (ESI), calcd for C₁₅H₁₄N₂O₂ (M + H⁺): 285.1159; found: 285.1164.

The slurry was resuspended in EtOH (20 mL) with 10% Pd/C and stirred under a hydrogen atmosphere (balloon). The catalyst was removed by filtration collected by filtration and washed with ice-cold absolute EtOH. The slurry was filtered and the solvent, rotary-evaporated. The residue was chromatographed (gradient; pentane/CHCl₃ 1:0 to 1:1) to give unsymmetrical spirobiquinoline 24a (219 mg, 73%) as an orange oil: IR ν = 3339, 2922, 2851, 1473, 1398, 797, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.79–7.74 (m, 1H), 7.69–7.66 (m, 1H), 7.43–7.38 (m, 2H), 7.22 (q, J = 8.4 Hz, 2H), 7.10–6.98 (m, 2H), 6.71 (td, J = 7.4, 1.2 Hz, 1H), 6.50 (dd, J = 8.1, 1.1 Hz, 2H).
1.0 mmol, 1.0 equiv) were converted into spirobiquinoline 20; 2-azido-4-(trifluoromethyl)benzaldehyde (215 mg, 1.0 mmol, 1.0 equiv) (15e) and 1-azido-2-naphthaldehyde (15b) (197 mg, 1.0 mmol, 1.0 equiv) were converted into spirobiquinoline 24b (206 mg, 56%), obtained as an orange oil: IR  $\nu = 3397, 2925, 1473, 1332, 1114, 799$ cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.79–7.75 (m, 2H), 7.60–7.64 (m, 1H), 7.43–7.39 (m, 2H), 7.26 (m, 1H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 1H), 6.94–6.89 (m, 1H), 6.72 (d, $J = 1.6$ Hz, 1H), 4.73 (s, 1H), 4.55 (s, 1H), 3.06 (t, $J = 6.8$ Hz, 2H), 3.01–2.89 (m, 2H), 2.18–1.95 (m, 4H); 13C NMR (101 MHz, CDCl$_3$) $\delta$ 142.8 (2C), 136.6, 133.3, 129.9, 128.9, 128.8, 128.0, 125.4, 125.2, 124.0, 123.1, 119.3, 118.1, 114.3, 114.1, 110.9, 64.1, 33.3, 32.6, 24.1, 23.6; HRMS (ESI), calcd for C$_{17}$H$_{16}$N$_2$Br$_2$ (M – H$^+$): 367.1422; found: 367.1428; microanalysis, calcd for C$_{17}$H$_{16}$N$_2$Br$_2$: C, 50.03; H, 25.00; Br, 15.01; N, 7.86.  

**Procedure for the Bromination of Spirobiquinoline 14a with NBS.** Freshly recrystallized NBS (700 mg, 4.0 mmol, 2.0 equiv or 1.0 mmol, 4.0 equiv) was added to one portion to spirobiquinoline 14a (500 mg, 2.0 mmol, 1.0 equiv) in MeCN (200 mL), with stirring, at 0 °C, and the resultant solution was allowed to warm to room temperature. After 16 h, the solvent was removed by rotary evaporation, and the resultant slurry, dissolved in CH$_2$Cl$_2$ and H$_2$O (1:1, 250 mL). The layers were separated, and the aqueous layer was further extracted with CH$_2$Cl$_2$ (2 × 100 mL). The combined organic extracts were dried (MgSO$_4$), the solvent was removed by rotary evaporation, and the residue was chromatographed (gradient; pentane/CH$_2$Cl$_2$ 1:0 to 4:1 to 1:1) to yield spirobiquinolines 25 and 26 as white solids. 

$6',6'-$Dibromo-3',3',4',4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (25). Using 2.0 equiv of NBS gave dibromide 25 (509 mg, 56%) as a white crystalline solid: mp 178–181 °C (CH$_2$Cl$_2$); IR $\nu = 3403, 2928, 1467, 1290, 856, 801$ cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.19 (d, $J = 2.3$ Hz, 2H), 7.11 (dd, $J = 8.5, 2.3$ Hz, 2H), 6.38 (d, $J = 8.5$ Hz, 2H), 4.25 (s, 2H), 2.87 (t, $J = 6.8$ Hz, 4H), 1.95 (m, 5H); 13C NMR (101 MHz, CDCl$_3$) $\delta$ 141.5 (2C), 131.7 (2C), 130.0 (2C), 122.2 (2C), 116.2 (2C), 109.5 (2C), 63.6, 32.8 (2C), 23.2 (2C); HRMS (ESI), calcd for C$_{32}$H$_{23}$N$_2$Br$_2$: 649.986 (M + H$^+$): 649.9860; found: 649.9874; microanalysis, calcd for C$_{32}$H$_{23}$N$_2$: C, 50.03; H, 3.95; N, 6.86; found: C, 50.17; H, 3.92; N, 6.63. 

$6',8',8'$-Tetramethyl-3',3',4',4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (26). Using 4.0 equiv of NBS gave tetrabromide 26 (830 mg, 74%) as a white crystalline solid: mp 172–173 °C (CH$_2$Cl$_2$); IR $\nu = 3397, 2831, 1691, 1480, 1449, 1173, 859$ cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (d, $J = 2.2$ Hz, 2H), 7.14 (d, $J = 2.2$ Hz, 2H), 4.80 (s, 2H), 2.88 (td, $J = 6.5, 1.5$ Hz, 4H), 2.06–1.96 (m, 2H), 1.93–1.82 (m, 2H); 13C NMR (101 MHz, CDCl$_3$) $\delta$ 138.7 (2C), 132.5 (2C), 130.9 (2C), 123.2 (2C), 109.3 (2C), 108.7 (2C), 64.8, 32.9 (2C), 23.9 (2C); HRMS (ESI), calcd for C$_{47}$H$_{50}$N$_2$: 830.484 (M + H$^+$): 830.4837; found: 830.4834; microanalysis, calcd for C$_{47}$H$_{50}$N$_2$: C, 78.12; H, 7.97; N, 10.06; found: C, 78.12; H, 8.12; N, 9.95. 

$1',1'$-Diallyl-3',3',4',4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (28b). Using the above general procedure, allyl bromide (38 µL, 0.44 mmol) gave the diallyl derivative 28b (53 mg, 80%) as a colorless oil: IR $\nu = 2942, 2845, 1641, 1490, 1458, 910, 743$ cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.09 (td, $J = 7.8, 1.7$ Hz, 1H), 7.01 (dd, $J = 7.3, 1.5$ Hz, 1H), 6.71–6.61
temperature and chromatographed (gradient; pentane/CH₂Cl₂ = 17.4, 5.6 Hz, 1H), 2.89
26.13, 25.00; HRMS (ESI), calc for C₃₀H₂₄N₂Br₂⁺Br⁺ (M + H⁺): 606.8236; found: 606.8163.

■ ASSOCIATED CONTENT
5 Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00482.
Selected research data is available from the data repository cited as ref 28
X-ray crystallographic data for selected compounds. Additional experimental procedures, crystallographic data, and ¹H and ¹³C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: agmb@ic.ac.uk.

ORCID
Anastasios Polyzos: 0000-0003-1063-4990

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS
We thank GlaxoSmithKline for the endowment (to A.G.M.B.), CSIRO for studentship support (for J.A.-T.), as well as Drs. Allred and Isabel Bader for their additional support.

■ REFERENCES
(1) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Curr. Opin. Chem. Biol. 2010, 14, 347–361.
(2) Lovering, F.; Bükker, J.; Humblet, C. J. Med. Chem. 2009, 52, 6752–6756.
(3) Sperry, J.; Wilson, Z. E.; Rathwell, D. C. K.; Brimble, M. A. Nat. Prod. Rep. 2010, 27, 1117–1137.
(4) Weingarten, D. M.; Li, N.; Ye, Z.; Meng, C. Q.; Ng, R.; Sikorski, J. A. Spiro Compounds for Treatment of Inflammatory Disorders. U.S. Patent 2008/0280974 A1, Nov 13, 2008.
(5) Freixa, Z.; Beentjes, M. S.; Batema, G. D.; Dieleman, C. B.; Van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; Frenae, J.; Goubitza, K.; Van Leuven, P. W. N. M. Angew. Chem., Int. Ed. 2003, 42, 1284–1287.
(6) Sala, X.; Garcia Suárez, E. J.; Freixa, Z.; Benet-Buchholz, J.; Van Leuven, P. W. N. M. Eur. J. Org. Chem. 2008, 2008, 6197–6205.
(7) Jacquet, O.; Clément, N. D.; Freixa, Z.; Ruiz, A.; Claver, C.; Van Leuven, P. W. N. M. Tetrahedron: Asymmetry 2011, 22, 1490–1498.
(8) Wang, X.; Dong, S.; Yao, Z.; Feng, L.; Daka, P.; Wang, H.; Xu, Z. Org. Lett. 2014, 16, 22–25.
(9) Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. ACS Catal. 2016, 6, 5747–5763.
(10) Cordes, J.; Murray, P. R. D.; White, A. J. P.; Barrett, A. G. M. Org. Lett. 2013, 15, 4992–4995.
(11) Loerbrooks, C.; Böker, B.; Cordes, J.; Barrett, A. G. M.; Thiel, W. Eur. J. Org. Chem. 2014, 2014, 5476–5486.
(12) Nycz, J. E.; Ceyt, K.; Szlachta, M.; Malecki, J. G.; Shaw, G.; Gilmore, B.; Jon, M. J. Mol. Struct. 2016, 1106, 416–423.
(13) Denisenko, S. N.; Pasch, E.; Kaupp, G. Angew. Chem., Int. Ed. 1999, 28, 1381–1383.
(14) Hubbs, J. L.; Heathcock, C. H. Org. Lett. 1999, 1, 1315–1317.
(15) Miura, Y.; Hayashi, N.; Yokoshiba, S.; Fukuyama, T. J. Am. Chem. Soc. 2012, 134, 11995–11997.
(16) Xu, Z.; Bao, X.; Wang, Q.; Zhu, J. Angew. Chem., Int. Ed. 2015, 54, 14937–14940.
(17) Attila, Y.; Heydenreich, M.; Ndakala, A.; Akala, H. M.; Kamau, E.; Yenesew, A. Phytochem. Lett. 2014, 10, 28–31.
(18) Umezara, A.; Ueda, H.; Tokuyama, H. Org. Lett. 2014, 16, 2526–2529.
(19) Feng, T.; Cai, X. H.; Liu, Y. P.; Li, Y.; Wang, Y. Y.; Luo, X. D. J. Nat. Prod. 2010, 73, 22–26.
(20) Xu, Z.; Wang, Q.; Zhu, J. J. Am. Chem. Soc. 2015, 137, 6712–6724.
(21) Wang, Q.; Tang, X.; Luo, X.; de Voogd, N. J.; Li, P.; Li, G. Org. Lett. 2015, 17, 3458–3461.
(22) Wang, X.; Han, Z.; Wang, Z.; Ding, K. Angew. Chem., Int. Ed. 2012, 51, 936–940.
(23) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y. J.; Liu, L.; Wang, Z.; Ding, K. Angew. Chem., Int. Ed. 2012, 51, 9276–9282.
(24) Wang, X.; Wang, X.; Guo, P.; Wang, Z.; Ding, K. Adv. Synth. Catal. 2013, 355, 2900–2907.
(25) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. J. Am. Chem. Soc. 2013, 135, 8197–8200.
(26) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. Org. Lett. 2010, 12, 2884–2887.
(27) Stokes, B. J.; Liu, S.; Driver, T. G. J. Am. Chem. Soc. 2011, 133, 4702–4705.
(28) Almond-Thynne, J.; White, A. J. P.; Polyzos, A.; Rzepa, H. R.; Parsons, P. J.; Barrett, A. G. M. Imp. Coll. Comput. Serv. Data Repository 2017, DOI: 10.14469/hpc/2099.
(29) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. Angew. Chem., Int. Ed. 2006, 45, 4635–4637.
(30) Irvine, J. L.; Hall, I. H.; Carlson, G. L.; Piantadosi, C. J. Org. Chem. 1972, 37, 2033–2034.
(31) Li, Q.; Chen, J.; Luo, S.; Xu, J.; Huang, Q.; Liu, T. Eur. J. Med. Chem. 2015, 93, 461–469.
(32) Boswell, G. E.; Licause, J. F. J. Org. Chem. 1995, 60, 6592–6594.
(33) Leroux, F.; Mangano, G.; Schlosser, M. Eur. J. Org. Chem. 2005, 2005, 5049–5054.
(34) Riesgo, E. C.; Jin, X.; Thummel, R. P. J. Org. Chem. 1996, 61, 3017–3022.
(35) Zhou, G.; Emerson, K.; Majusiak, E.; Anderson, C.; Sudah, O. Org. Process Res. Dev. 2012, 16, 204–213.