Stereoselective Synthesis of Spiro-Decalin Oxindole Derivatives via Sequential Organocatalytic Michael−Domino Michael/Aldol Reaction

Leonardo Straminelli, Francesco Vicentini, Antonio Di Sabato, Carmela Maria Montone, Chiara Cavaliere, Kari Rissanen, Francesca Leonelli, and Fabrizio Vetica*

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ABSTRACT: A highly stereoselective procedure for the synthesis of spiro-polycyclic oxindoles bearing five contiguous stereogenic centers including two tetrasubstituted carbons has been developed. Under sequential organocatalysis performed by a pyrrolidine-based organocatalyst and DBU, a highly atom-economical Michael−domino Michael/aldol reaction sequence was optimized, yielding variously functionalized spiro-decalin oxindoles with excellent stereoselectivity (>99:1 dr, up to 92% ee).

The asymmetric synthesis of complex heterocyclic scaffolds with multiple stereocenters in a stereoselective fashion represents one of the major challenges in modern organic chemistry. In the past two decades, many research groups have devoted their efforts in the exponential development of asymmetric organocatalysis, as an environmentally friendly and robust approach to achieve this aim. In fact, organocatalysts are usually stable in air and moisture and are characterized by a variety of possible activation modes of different functional groups.

In combination with the always-growing necessity for practically simple and eco-friendly synthetic procedures, asymmetric organocatalytic one-pot sequential reactions proved to be an effective and efficient approach toward the generation of structurally diverse molecular architectures from readily available starting materials.

The oxindole framework is a common scaffold in a plethora of natural and synthetic substances with various biological activities. In the realm of oxindole derivatives, of particular interest are spirocyclohexane oxindoles, which exhibit potential pharmaceutical applicability as, for instance, gelsamin (A) a glycine receptor agonist, anticancer compound B discovered by Hoffman-La Roche, or Satavaptan (C), a vasopressin-2-receptor agonist.

Within this context, synthetic organic chemists have studied and optimized many protocols for the stereoselective organocatalytic synthesis of oxindoles derivatives. The most common route to achieve spirocyclic oxindoles relies on the use of 3-alkylidene-oxindoles, prepared straightforwardly by olefination of isatins, often commercially available 3-oxo-oxindoles.

Because of our continuing interest in asymmetric organocatalytic methodologies toward valuable chiral building blocks and structurally diverse heterocycles, we envisioned the possibility to design a sequential organocatalytic protocol toward polyfunctionalized spiro-decalin oxindoles derivatives, starting from cyclohexanone (1), nitrostyrenes 2, and 3-alkylideneoxindoles 3 (Figure 1, b). Indeed, the activation of

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cyclohexanone (1) via enamine formation to undergo Michael addition to an electron-poor olefin has become a key starting point for cascade reactions. Having selected two different Michael acceptors, such as 2 and 3, we opted for a one-pot protocol, in order to control the regioselectivity of the reaction sequence by simple operational setup. Subsequently, the initial conjugate addition could be followed by a second Michael addition on the 3-alkylidene oxindoles 3, which would then lead to a ring-closing aldol reaction and generate the spirodecalin moiety bearing 5 contiguous stereocenters, two of which are quaternary.

Our investigation started with the preparation of the Michael adduct 4a, employing L-proline (C1, 50 mol %) as catalyst and equimolar amounts of substrates 1 and 2a on a 3 mmol scale. Indeed, the organocatalyzed Michael reaction between these substrates has been largely investigated, and on the basis of the literature reports, we initially opted for an economical and operationally simple proline-catalyzed Michael reaction to get a considerable amount of product 4a, to further investigate the envisioned reaction sequence. Intermediate 4a was isolated and purified with 81% yield, >99:1 dr, and 52% ee.

Afterward, it was used in an initial test reaction with substrate 3a in the presence of DBU (30 mol %) as basic organocatalyst in MeOH, to promote the domino Michael/aldol reaction (Table 1, entry 1).

Despite product 5a being isolated with a poor yield of 6%, this initial outcome was extremely promising. Indeed, not only did it confirm the possibility to achieve the desired spirodecalin oxindole scaffold, with the envisaged reaction sequence, but also it could be observed that the domino Michael/aldol reaction was extremely diastereoselective, leading to the final product with 5 contiguous stereocenters as a single diastereoisomer (>99:1 dr). With these outcomes in hand, we focused on the optimization of the reaction conditions by varying the solvent and the amount of base used (Table 1, entries 2–12). With our delight, we were able to increase the yield of the reaction to 58% (74% average yield considering the two reaction steps) while maintaining the same level of diastereoselectivity, by using CH2Cl2 as solvent and 30 mol % of DBU (Table 1, entry 2).

It is worth mentioning that in all the tested cases we observed complete retention of the enantiomeric excesses (ee) from substrate 4a, excluding any possible base-promoted racemization. With this in mind, we decided to focus our efforts on the optimization of the reaction conditions in the synthesis of intermediate 4a to maximize the enantioselectivity, which would then be retained in the subsequent synthesis of the final product. As mentioned above, many organocatalytic protocols to achieve 4a have been reported, furnishing excellent diastereo- and enantiocontrol. Nevertheless, in many cases the catalysts’ synthesis requires numerous reaction steps and tedious and harsh reaction conditions. Moreover, in order to reach high yields, 3 to 10 equiv of cyclohexanone are used. Consequently, envisioning an economical and environmentally friendlier synthetic procedure, we started a thorough screening of various readily available secondary amine-based organocatalysts, using methanol as solvent and keeping the substrate ratio to 1:1 equiv (Table 2, entries 1–11). The best results were obtained by using commercially available (25′,2′S)-2,2′-bipyrrrolidine C9, used directly as tartrate salt (Table 2, entry 10). To our delight, the Michael adduct 4a was isolated with 35% yield, >99:1 dr and 92% ee. Due to the chirality of L-tartaric acid, we decided to evaluate a possible involvement of tartrate counterions in the enantiocontrol. Thus, an additional trial was performed by initial treatment of the C9 salt with base, to remove the tartrate. Probing the newly obtained secondary amine catalyst, we observed the formation of the desired product with a lower yield, but with a similar level of enantiomeric excess, confirming that only the bis-pyrroldine scaffold is responsible for the enantiocontrol (92% ee, 16% yield, Table 2, entry 11). Additionally, these results corroborate the many literature findings in which an acidic additive increases the reactivity of cyclohexanone, favoring the enamine formation. Therefore, the simultaneous presence of the active chiral bipyrrrolidine core and the acid additive in this commercially available catalyst represents a practical and economic advantage.

Further optimization involving catalyst C9 has been carried out by analyzing the effect of both solvents and catalyst loading on the reaction outcomes (Table 2, entries 12–20). By changing from the initially used MeOH to iPrOH or CH2Cl2, we did not observe significant changes in the diastereoselectivity (dr >99:1); nevertheless, both the yield and enantioselectivity decreased considerably (Table 2, entries 12 and 15). Subsequently we tested the effects of less polar solvents, but in almost all cases both yields and enantiocontrol were significantly lowered. Further screening of the catalyst loading led to the identification of the best reaction conditions using 20 mol % of C9 to provide 35% yield, >99:1 dr, and 92% ee (Table 2, entry 10).

Table 1. Step-by-Step Approach: Optimization of the Reaction Conditions for the Domino Michael/Aldol Reaction

| entry | solvent | DBU [mol %] | yield [%] |
|-------|---------|-------------|-----------|
| 1     | MeOH    | 30          | 6 (25)    |
| 2     | iPrOH   | 30          | 58 (74)   |
| 3     | CH2Cl2  | 30          | 33 (57)   |
| 4     | CHCl3   | 30          | 41 (64)   |
| 5     | Hexane  | 30          | 10 (32)   |
| 6     | Et2O    | 30          | 45 (67)   |
| 7     | CAN     | 30          | 18 (42)   |
| 8     | THF     | 30          | 35 (50)   |
| 9     | CH2Cl2  | 20          | 51 (71)   |
| 10    | CH2Cl2  | 40          | 16 (40)   |
| 11    | CH2Cl2  | 50          | 16 (40)   |
| 12    | CH2Cl2  | 100         | 4 (20)    |

*Unless otherwise stated, a solution of 1 (3 mmol, 1.0 equiv) and 2a (3 mmol, 1.0 equiv) in MeOH (8 mL, 0.125 M) was stirred at rt in the presence of l-proline (50 mol %) for the indicated time. Product 4a was isolated, and afterward, to a solution of 4a (0.1 mmol), 3a (0.1 mmol) and DBU (30 mol %) were added, and the reaction mixture was stirred for 4 d. In all experiments the dr values were determined via 1H NMR analysis, and the ee values via HPLC analysis on a chiral stationary phase. Isolated yields after flash column chromatography. Values in brackets correspond to the average yield per step.
Table 2. Catalyst Screening and Reaction Condition Optimization for the Michael Addition of Cyclohexanone to Nitrostyrene

| entry | cat. solvent | cat. loading [mol %] | yield [%] | dr [%] | ee [%] |
|-------|--------------|----------------------|-----------|--------|--------|
| 1     | C1 MeOH      | 20                   | 81        | >99:1  | 52     |
| 2     | C2 MeOH      | 20                   | n.r.      |        |        |
| 3     | C3 MeOH      | 20                   | n.r.      |        |        |
| 4     | C4 MeOH      | 20                   | n.r.      |        |        |
| 5     | C5 MeOH      | 20                   | 99        | >99:1  | 62     |
| 6     | C6 MeOH      | 20                   | 25        | >99:1  | 82     |
| 7     | C7 MeOH      | 20                   | n.r.      |        |        |
| 8     | C8 MeOH      | 20                   | n.r.      |        |        |
| 9     | C9 MeOH      | 20                   | n.r.      |        |        |
| 10    | C9 MeOH      | 20                   | 35        | >99:1  | 92     |
| 11    | C9 MeOH      | 20                   | 16        | >99:1  | 92     |
| 12    | C9 iPrOH     | 20                   | 12        | >99:1  | 90     |
| 13    | C9 ACN       | 20                   | 20        | >99:1  | 60     |
| 14    | C9 THF       | 20                   | 8         | >99:1  | 16     |
| 15    | C9 CHCl₂     | 20                   | 16        | >99:1  | 72     |
| 16    | C9 CHCl₃     | 20                   | 4         | n.d.   | n.d.   |
| 17    | C9 Et₂O      | 20                   | 8         | >99:1  | 6      |
| 18    | C9 hexane    | 20                   | 6         | n.d.   | n.d.   |
| 19    | C9 MeOH      | 30                   | 34        | >99:1  | 92     |
| 20    | C9 MeOH      | 50                   | 36        | >99:1  | 92     |

“A solution of 1 (0.1 mmol, 1.0 equiv) and 2a (0.1 mmol, 1.0 equiv) in MeOH (1 mL) was stirred at rt in the presence of the specified catalyst for the indicated time. bIsolated yields after flash column chromatography. cDetermined via 1H NMR analysis. dDetermined via HPLC analysis on a chiral stationary phase. eReaction carried out in the presence of 20 mol % PhCO₂H. fCatalyst was pretreated with base and extracted to neutralize the ammonium salt and remove tartrate.

Once we identified the optimal conditions for both the initial Michael reaction between 1 and 2 and the subsequent DBU-promoted domino Michael/aldol sequence, we envisioned the possibility of performing the three steps in a one-pot protocol.

Since the two sequential reactions are optimized in different solvents, we tested the possibility of replacing the solvent after the first Michael reaction, followed by the addition of 3 and DBU (30 mol %). Unfortunately, the desired final compound 5a was isolated, while a complex mixture of products was detected. We performed some more trials varying the amount of DBU, to neutralize the 20 mol % tartaric acid present in the reaction mixture due to the catalyst; however, this strategy was also unsuccessful.

We believe that the presence of unreacted starting materials (1 and 2) could interfere with the domino Michael/aldol sequence and lead to the formation of other side-products.
Scheme 2. Substrate Scope of the Sequential Michael–Domino Michael/Aldol Reaction \( ^{4, h, c, d} \)

This outcome could be explained by the acidity of this site, which would interfere with the action of the DBU in promoting the domino reaction sequence. Nevertheless, even performing the reaction with an excess of DBU did not lead to the detection of the final product. Thus, we opted for a further variation of the N-protection with a Boc group. Unfortunately the presence of this protecting group did not lead to the final product. A complex mixture of products of difficult identification was isolated instead, presumably due to an in situ deprotection of the Boc group or by decomposition of the alkylidene/intermediate by lactam ring opening.

Finally, an additional functional group variation was considered; particularly, we introduced an N–Et group instead. With our delight, the reaction also worked straightforwardly with this alkyl substitution, with similar excellent results to the N–Me ones in terms of stereoselectivity, despite slightly lower yields.

The absolute configuration was unambiguously determined by X-ray crystal structure analysis of compound 5a, and by analogy the configuration of all other products was assigned accordingly (Scheme 2). \( ^{36} \)

In conclusion, we developed an efficient and atom-economical methodology for the synthesis of highly functionalized spiro-decalin oxindole derivatives employing a stereoselective organocatalytic Michael–domino Michael/aldol reaction sequence. We observed good yields for a domino transformation (13–79%), which correspond to an average yield per step ranging from 36 to 89%. During this process, 5 new stereocenters are generated with virtually complete diastereoselectivities (>99:1 d.r) and excellent enantioselectivities (92% ee), under mild and practically simple reaction conditions. Due to the importance of spiro-oxindoles in medicinal chemistry, the presence of easily modifiable groups and the high enantioselectivity could lead the way for late-stage functionalization in the search of potentially bioactive compounds.

## EXPERIMENTAL SECTION

### General Information

Unless otherwise noted, all commercially available compounds were used without further purification. For preparative column chromatography SIL G-25 UV252 from Macherey-Nagel, particle size 0.400–0.63 mm (230–240 mesh flash) was used. Visualization of the developed TLC plates was performed with UV irradiation (254 nm). Optical rotations were measured on a DIP-370 Jasco polarimeter. GC-MS analyses were performed using an Agilent HP 5892 series II GC (phenyl silicone column 30 m × 0.25 mm × 0.5 mm) coupled with a mass spectrometer HP 5972 MSD operating at 70 eV. Elution program: initial T = 100 °C for 4 min, increasing the T at 10 °C/min rate, up to 250 °C. MS were by directly infusing solutions with a concentration of 1 ng μL\(^{-1}\) prepared in methanol at a flow rate of 10 μL min\(^{-1}\).

For both ion modes, the full-scan MS acquisition range was 130–1000 m/z, the resolution was set to 35000 (full width at half-maximum, fwhm, @200 m/z). The mass spectrometer was externally calibrated every 48 h, within a mass accuracy of 1 ppm, using the commercial Pierce positive and negative calibration solutions (Thermo Fisher Scientific). Raw data files were acquired by Xcalibur software (version 3.1, Thermo Fisher Scientific). \(^1\)H and \(^13\)C{\(^1\)H} NMR spectra were recorded on Bruker Avance or 400 or 300 spectrometers. Analytical HPLC was performed on a Shimadzu LC-20AD HPLC instrument equipped with a PDA detector (Shimadzu SPD-M20A) and a refractive index detector (Shimadzu RID-20A), using chiral stationary phases (Chiralpak IA). For the preparation of racemic compounds, a mixture of \(\alpha\)-proline and \(\gamma\)-proline was used.

### General Procedure for the Synthesis of N-Benzylisatins

To a solution of \(\text{isatin (1.0 mmol, 1.0 equiv)}\) and \(\text{Na}_2\text{CO}_3\) (3.0 mmol, 3.0 equiv) in 8 mL of acetonitrile (0.125 M), benzyl bromide was added (1.0 mmol, 1.0 equiv). The mixture was stirred under reflux for 24 h using an oil bath and afterward allowed to cool to room temperature. Then, the solvent was evaporated under reduced pressure, and the crude residue was dissolved in AcOEt and extracted with a basic aqueous solution of \(\text{Na}_2\text{CO}_3\). The combined organic phases were dried (MgSO\(_4\)), filtered, and then concentrated under reduced pressure. The product was isolated after flash chromatography on silica gel.

Unless otherwise stated, the compounds were prepared following this procedure and all the analytical data were in accordance with the literature reports. \(^{37,38}\)

\(1-(4\text{-Bromobenzyl})\text{indoline-2,3-dione}\). Prepared from the general procedure using 4-bromobenzyl bromide as substrate. The analytical data are in accordance with the literature data. \(^{39,40}\)

### General Procedure for the Synthesis of N-Methylisatins

Prepared following a reported procedure starting from commercially available isatins. \(^{41}\) Unless otherwise stated, the compounds were prepared following this procedure and all the analytical data were in accordance with the literature reports. \(^{42,43,44}\)
General Procedure for the Synthesis of N-Ethylisatins.
Prepared following a reported procedure starting from commercially available isatin.s\textsuperscript{45} Unless otherwise stated, the compounds were prepared following this procedure and all the analytical data were in accordance with the literature reports. To a solution of isatin (1.0 mmol, 1.0 equiv) and K$_2$CO$_3$ (1.5 mmol, 1.5 equiv) in 3 mL of DMF (1 M), ethyl bromide was added (1.1 mmol, 1.1 equiv). The mixture was stirred for 12 h at room temperature. After TLC monitoring, cold water was added (20 mL) and a red suspension was formed. Then, after filtration and washing with water, a red solid is obtained. Unless otherwise stated, the compounds were prepared following this procedure and all the analytical data were in accordance with the literature reports.

General Procedure for the Synthesis of 2-(2-Oxindolin-3-ylidene)malononitrile (3). To a solution of N-protected isatin (1.0 mmol, 1.0 equiv) in 10 mL EtOH (0.1 M), malononitrile (1.0 mmol, 1.0 equiv) was added and the mixture was stirred at reflux for 3 h using an oil bath. Afterward, the formed suspension was filtered to isolate a deep red/purple solid. The solid product was washed with cold ethanol and then dried. No further purification was needed. Unless otherwise stated, the compounds were prepared following this procedure and all the analytical data were in accordance with the literature reports.

2-(4-Bromobenzyl)-2-(2-oxindolin-3-ylidene)malononitrile (3a). The product has never been reported before so a complete characterization is reported. Prepared on a 3.0 mmol scale following this procedure and all the analytical data were in accordance with the literature reports. Prepared on a 3.0 mmol scale following this procedure and all the analytical data were in accordance with the literature reports.

Asymmetric Scaled-up Organocatalytic Synthesis of Michael Intermediate 4a. To a solution of cyclohexanone (1 3.0 mmol, 1.0 equiv) in MeOH (8.0 mL, 0.125 M) were added the nitrostyrene 2a (3.0 mmol, 1.0 equiv) and the catalyst C9 (0.6 mmol, 20 mol %), and the mixture was stirred at room temperature for 10 days. After the elapsing time, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired (S)-2-(R)-2-nitro-1-phenylethyl)cyclohexan-1-one 4a as a colorless solid. 281 mg of the final product were isolated (38% yield, 92% ee, \( \tau_{\text{major}} = +8.5 \) (c 1.1, Cl$_2$CH$_2$I) mp 190–192 °C. H NMR (400 MHz, CDCl$_3$) \( \delta = 8.77 \) (dd, \( J = 2.0, 13.9 \) Hz, CH$_{\text{arom}}$), 7.49–7.26 (m, 9H, CH$_{\text{arom}}$), 7.11–7.07 (m, 1H, CH$_{\text{arom}}$), 6.68 (dd, \( J = 3.1, 13.9 \) Hz, CH$_{\text{arom}}$), 6.71 (d, \( J = 8.5, 13.9 \) Hz, CH$_{\text{arom}}$), 5.46 (d, \( J = 11.9, 13.9 \) Hz, CH$_{\text{arom}}$), 5.07 (d, \( J = 15.7, 13.9 \) Hz, CH$_{\text{arom}}$), 4.95 (d, \( J = 15.7, 13.9 \) Hz, CH$_{\text{arom}}$), 4.16 (s, \( J = 11.9, 13.9 \) Hz, CH$_{\text{arom}}$), 2.38 (tt, \( J = 11.9, 3.0 \) Hz, CH$_{\text{arom}}$), 2.27–2.18 (m, 1H, CH$_{\text{arom}}$), 1.97 (tt, \( J = 12.1, 3.4 \) Hz, CH$_{\text{arom}}$), 1.93–1.80 (m, 1H, CH$_{\text{arom}}$), 1.74–1.50 (m, 4H, CH$_{\text{arom}}$, CH$_{\text{CH}}$, OH), 1.32–1.15 (m, 2H, CH$_{\text{arom}}$) ppm. \( ^{13}\text{C}(^{1}\text{H}) \) NMR (101 MHz, CDCl$_3$) \( \delta = 173.3, 142.3, 134.9, 133.5, 132.2, 131.3, 129.5, 129.2, 129.1, 128.7, 123.4, 125.4, 124.8, 124.6, 121.6, 130.3, 111.0, 110.3, 92.4, 78.5, 54.7, 53.4, 50.4, 45.9, 45.6, 43.1, 37.1, 25.2, 20.8 ppm. HR-MS (ESI$^+$) m/z calc'd for [M$^{+}$]$^{+}$ = 314.0806; found 314.0802.

General Procedure for the Organocatalytic Stereoselective Domino Michael/Aldol Reaction (5). To a solution of 4 (0.1 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1.0 mL, 0.1 M) were added the alkyldiene 3 (0.1 mmol, 1.0 equiv) and DBU (4.5 µL, 0.03 mol, 30 mol %), and the mixture was stirred for 4 d. After the elapsing time, the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography to give the desired product 5.

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was isolated after flash chromatography on silica gel (H/EtOAc 6:4) as a colorless solid (19 mg, 40% yield, >99:1 dr, 92% ee). Molecular formula: C_{18}H_{22}NO_3. Molecular mass: 470.53 g mol^{-1}. HPLC: IA, hexane/iPrOH 95:5, 1.0 mL/min, dr >99:1, \( \tau_{min} = 8.8 \) min; OR: [\( \alpha \)]D^{20} = +12.0 (c 1.0, CHCl_3) mp 111.0–112.0 °C. H NMR (300 MHz, CDCl_3) \( \delta = 7.67 \) (d, \( J = 1.4 \) Hz, 1H), 7.47–7.27 (m, 13H), 7.16–7.05 (m, 3H), 6.67 (d, \( J = 8.1 \) Hz, 1H), 5.49 (d, \( J = 12.0 \) Hz, 1H), 5.07 (d, \( J = 15.8 \) Hz, 1H), 4.98 (d, \( J = 15.8 \) Hz, 1H), 4.18 (t, \( J = 11.9 \) Hz, 1H), 2.36 (4H, s, 4H), 2.22 (d, \( J = 11.0 \) Hz, 1H), 2.04–1.81 (m, 2H), 1.66 (d, \( J = 15.0 \) Hz, 2H), 1.28 (s, 3H) ppm. 13C{H} NMR (101 MHz, CDCl_3) \( \delta = 173.2, 139.9, 135.0, 134.8, 133.7, 132.5, 131.3, 129.4, 129.0, 128.7, 128.2, 124.9, 121.6, 111.0, 110.4, 92.4, 82.3, 78.4, 54.7, 50.5, 47.3, 45.9, 45.5, 43.1, 37.1, 31.6, 29.7, 25.2, 21.3, 20.8 ppm. HR-MS (ESI) m/z calc. for \([\text{M} + \text{H}]^+ = C_{18}H_{21}NO_3\): 473.1240, found 473.1240.

(3S,5'R,4a'R,8a'S)-1-Benzyl-8a'-hydroxy-5-methyl-3'-nitro-2-oxo-4'-phenyl-3',4'a',5',6',7',8'-8a'-octahydro-1'H-8-spiro(indole-3,2'-naphthalene)-1',1'-dicarboximide (5e). The product 5e was isolated after flash chromatography on silica gel (H/EtOAc 6:4) as a colorless solid (9 mg, 17% yield, >99:1 dr, 92% ee). Molecular formula: C_{19}H_{23}NO_3. Molecular mass: 484.56 g mol^{-1}. HPLC: IA, hexane/iPrOH 95:5, 1.0 mL/min, dr >99:1, \( \tau_{min} = 6.4 \) min; OR: [\( \alpha \)]D^{20} = +7.5 (c 0.73, CHCl_3) mp 232–233 °C. H NMR (300 MHz, CDCl_3) \( \delta = 7.67 \) (s, 1H), 7.42 (d, \( J = 14.2 \) Hz, 1H), 7.07 (s, 1H), 6.84 (d, \( J = 8.1 \) Hz, 1H), 5.45 (d, \( J = 11.9 \) Hz, 1H), 4.13 (t, \( J = 12.0 \) Hz, 1H), 2.03 (d, \( J = 14.2 \) Hz, 1H), 1.95 (s, 9H, CH_3Ph), 2.34 (2H, s, 4H) ppm. 13C{H} NMR (75 MHz, CDCl_3) \( \delta = 170.2, 141.3, 134.3, 134.2, 132.5, 132.5, 129.2, 128.9, 128.5, 125.9, 122.1, 112.5, 109.8, 92.0, 77.9, 54.3, 49.9, 45.4, 42.6, 36.9, 29.7, 24.8, 20.9, 20.4 ppm. HR-MS (ESI) m/z calc. for \([\text{M} + \text{H}]^+ = C_{20}H_{18}N_3O_8\): 485.2183, found 485.2187.
Accession Codes
CCDC 2165719 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author
Fabrizio Vetica − Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy; orcid.org/0000-0002-7171-8779; Email: fabrizio.vetica@uniroma1.it

Authors
Leonardo Straminelli − Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy
Francesco Vicentini − Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy
Antonio Di Sabato − Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy
Carmela Maria Montone − Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy
Chiara Cavaliere − Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c01046

Author Contributions
§L.S. and F.V. contributed equally to the work

Notes
The authors declare no competing financial interest.

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