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(−)-Astrogorgiadiol: a shorter route to A-ring synthon

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ABSTRACT

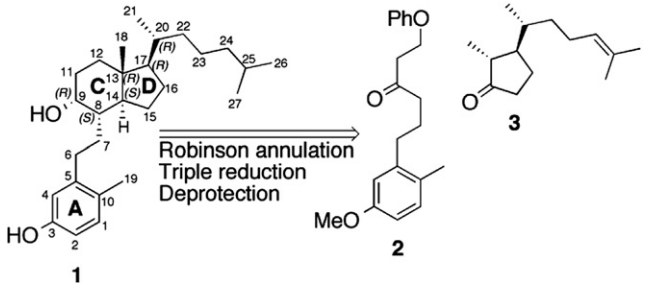
A new route to the key A-ring/C-ring precursor synthon of (−)-astrogorgiadiol is described, for the strategy based on Robinson annulation. This synthon is also key for the synthesis of other related calicoferols and astrogorgols. The route takes full advantage of the opening of 6-methoxy-1-tetralol with bis(*sym*-collidine) bromine(I) triflate. It involves a new protection–deprotection sequence of an enone. It is the shortest synthesis to date, consisting of seven steps.

1. Introduction

(−)-Astrogorgiadiol **1**, a 9,10-secosteroid of marine origin[1] discovered by Fusetani's team in 1989[2] has since been the object of great interest due to its unique property of osteopontin down-regulation.[3] Osteopontin seems indeed a privileged target as this protein plays a key-role in metastatic diseases, such as cancers,[4] in demyelinating diseases, such as multiple sclerosis,[5] in the development of virulent asthma,[6] and in osteoporosis.[7] Moreover, recently reported in vitro bioassays towards 16 human tumour related protein kinases comparing (−)-astrogorgiadiol, calicoferols and astrogorgols showed inhibitions in the micromolar range against important kinases involved in cancer development.[8]

Two strategies have been developed by organic chemists for the synthesis of this molecule. De Riccardis' team chose a C-6–C-7 disconnection and implemented a semisynthetic route using Grundmann's ketone, obtained from (+)-vitamin D_3.[9] Taber's team designed a total synthesis featuring as the key step a Robinson annulation between the A-ring/C-ring precursor synthon **2** and the D-ring synthon **3** (Scheme 1).[10]

The recent publication in this journal by Taber et al.[11] of a second generation synthesis of this A-ring synthon prompts us to report the successful shorter synthesis of an equivalent of this key intermediate, using the opening of alcohol **5**.



Scheme 1. Taber's retrosynthetic analysis.

This synthon is of key importance not only for the synthesis of (−)-astrogorgiadiol, but also for the growing family of 9,10-secosteroids[1,8]—calicoferols, astrogorgols—which exhibit promising inhibitory activities and will therefore attract more and more attention.

2. Results and discussion

2.1. A new reagent to open tetralols

Rousseau et al. demonstrated that $Br^+(symcoll)_2PF_6^-$ (BBH) opens 6-methoxy-1-tetralol.[12] The product of this reaction

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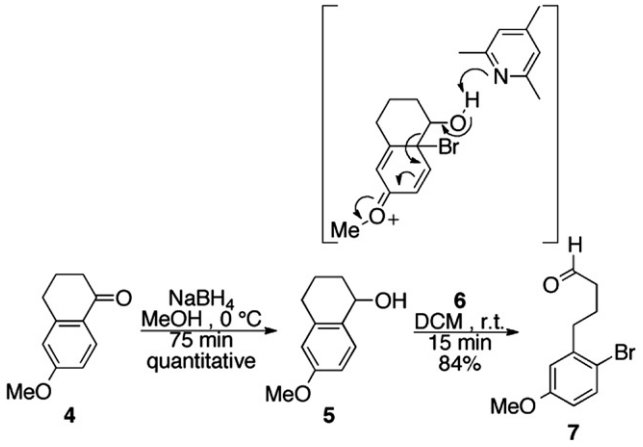
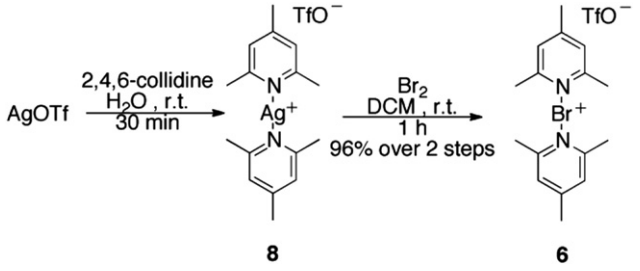
constitutes a fairly advanced intermediate en route to the A-ring synthon, which we decided to exploit. Commercially available $I^+(symcoll)_2PF_6^-$ failed to provide the iodo compound, but we discovered that $Br^+(symcoll)_2TfO^-$ **6** is as efficient as BBH and **7** was obtained efficiently in two steps starting from the commercially available 6-methoxy-1-tetralone **4** (Scheme 2).



Scheme 2. Tetralol opening with $Br^+(symcoll)_2TfO^-$ **6**.

Reagent **6**, already described by Brown's team,[13] was synthesized according to Rousseau's procedure, starting from silver triflate, allowing atom economy[14] compared to BBH (Scheme 3). It acts as a bromonium donor, which is attacked by the aryl electrons thanks to the donating effect of the methoxy group *para*. The collidine then abstracts the hydrogen of the alcohol in an acid/base reaction; the opening of the tetralol follows as the density of electrons is displaced to produce the ketone and the aromaticity is restored (Scheme 2).

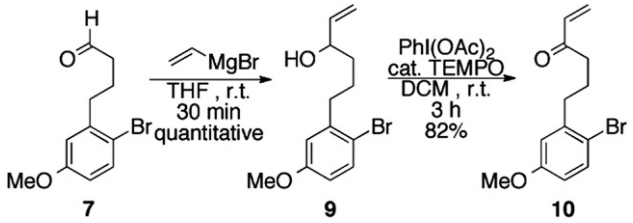


Scheme 3. Preparation of $Br^+(symcoll)_2TfO^-$ **6**.

With the intermediate **7** in hand, the building of A-ring synthon had to include the installation of Me-19 on the aromatic ring and the construction of the conjugated ketone.

2.2. Construction of the conjugated ketone: the C-ring precursor

The aldehyde **7** was reacted with vinylmagnesium bromide to obtain the allylic alcohol **9** quickly and in quantitative yield (Scheme 4). Oxidation of the latter with manganese dioxide or PDC or PCC gave poor yields. Hence, a procedure with TEMPO/iodobenzene diacetate in dichloromethane[15] was preferred. This



Scheme 4. Securing the allylic ketone **10**.

oxidation proved very convenient and could be performed under an atmosphere of air to secure **10**.

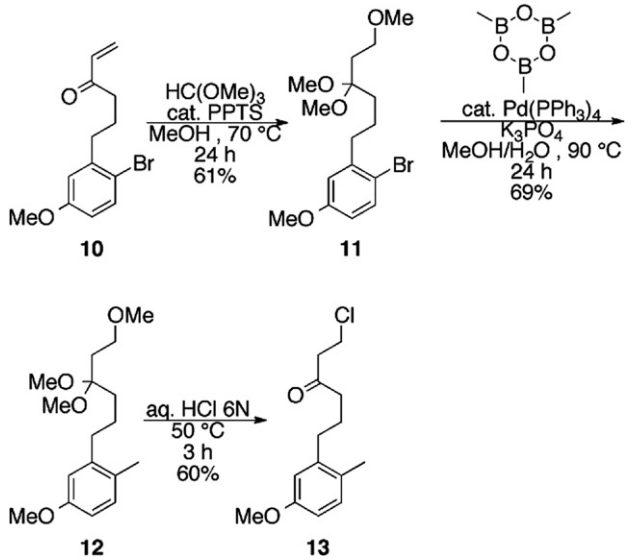
2.3. Installing the methyl group Me-19

The second part of the construction was the installation of the Me-19. This methylation could be envisioned at different stages, on the aryl bromides **7**, **9** or **10**. Different conditions and types of reactions were attempted but none gave the expected methylated product (Table 1).

Table 1
Failed attempts of methylation at C-10

Substrate	Coupling type	Conditions
7	Stille	Me_4Sn, $PdCl_2(CH_3CN)_2$, Ph_3As, CuI, Et_3N, DMF
9	Kumada	MeMgBr, $NiCl_2(PPh_3)_2$, THF
9	Substitution	MeLi, Et_2O
9	Suzuki	Trimethylboroxine, $PdCl_2(dppf)$, K_2CO_3, H_2O, dioxane
10	Stille	Me_4Sn, $PdCl_2(CH_3CN)_2$, Ph_3As, CuI, Et_3N, DMF
10	Suzuki	Trimethylboroxine, $PdCl_2(dppf)$, K_2CO_3, H_2O, DMF
10	Suzuki	Trimethylboroxine, $Pd(PPh_3)_4$, Et_3N, DMF
10	Stannation	$(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene

It was therefore necessary to use a protection–deprotection sequence. We chose to protect the ketone using trimethyl orthoformate. What we obtained using a common procedure was the protection of both the alkene and ketone of **10** (Scheme 5).



Scheme 5. Installation of the methyl in *ortho* via Suzuki-type reaction (with new protection–deprotection sequence).

The reaction is not unprecedented: it was performed on ethyl vinyl ketone to obtain 1,3,3-trimethoxypentane by Ansell et al.,[16] but, to the best of our knowledge, it was never used as a protection previously. The trimethoxy compound **11** could then be reacted with trimethylboroxine in a Suzuki-type reaction to get the methylated aryl product **12** (Scheme 5). The use of methanol/water 1:1 as solvent proved to minimize the reduction of aryl bromide **11** during Suzuki coupling with trimethylboroxine.[17] Trimethylboroxine is not so commonly used for methylation, but its advantages are wide. It is rather stable and cheaper than methylboronic acid. Such a reagent, used in Suzuki couplings, makes it possible to avoid using less convenient methyl Grignard reagents. Deprotection with aqueous HCl yielded the A-ring synthon **13**, analogous to **2**, ready for Robinson annulation.

3. Conclusion

We have discovered a concise route (seven linear steps, 17.4% yield) to the A-ring/C-ring precursor synthon of (−)-astrogorgiadiol, taking advantage of the opening of 6-methoxy-1-tetralol with bis(*sym*-collidine) bromine(I) triflate. The challenging methylation at C-10 (Me-19) fostered the development of a new protection–deprotection sequence of the enone (converted in 9,9,12-trimethoxy). This synthesis constitutes a valuable tool for the exploration of calicoferols, astrogorgols and analogues.

4. Experimental section

4.1. General

All starting materials were obtained commercially from Aldrich, Avocado, Acros, Lancaster, BDH or Strem and used without further purification. All solvents were dried prior to use except when indicated otherwise. Flash chromatography was conducted using Merck silica gel 60 (40–60 μm). TLC was carried out on pre-coated glass-backed plates (Merck Kiesel-gel 60 F_{254}), visualized at 254 nm and stained with anisaldehyde or phosphomolybdic acid. Infra-red (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. The wave number is given in cm^{-1} with peak intensity signified as s, m and w for strong, medium and weak, respectively. Mass spectra (FAB, CI or EI) were recorded at the Departmental Mass Spectrometry Service of the University College London on a VG Analytical 70S instrument by Dr. Lisa Harris and John Hill. Proton Nuclear Magnetic Resonance spectra were recorded on Bruker AMX-500, 400 or 300 NMR Spectrometers. The NMR spectra were recorded with reference to the residual solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). ^{13}C DEPT, HMQC, HMBC and COSY were used to determine structures. In the description of the spectra, the numbering of the carbon atoms refers to the numbering that the carbon atoms would have in (−)-astrogorgiadiol (steroids numbering) as seen in Scheme 1.

4.2. Bromonium bis(*sym*-collidine)triflate (6)

2,4,6-Collidine (25 mL, 189 mmol) was added dropwise over 30 min to a solution of silver triflate (19.4 g, 75.5 mmol) in water (125 mL) maintained at rt by a water bath. The mixture was then filtered and the white solid (Ag^+(*sym*-collidine)$_2TfO^-$) was washed with water (2×50 mL) and dried in a desiccator with P_2O_5 under vacuum over the weekend. The complex was then dissolved in DCM (250 mL). Bromine (3.9 mL, 75.5 mmol) was then added dropwise to the solution under nitrogen, maintained at rt by a water bath. After 1 h, the mixture was filtered to remove the precipitate of AgBr, which was washed with ether (3×100 mL). The combined filtrate was concentrated under vacuum to yield 96% **6** (34.0 g, 72.1 mmol) over the two steps as a white solid. The spectroscopic data matched that reported.[13]

4.3. 6-Methoxy-1-tetralol (5)

Sodium borohydride (4.54 g, 120 mmol) was added portionwise to a solution of 6-methoxy-1-tetralone (7.05 g, 40 mmol) in methanol (130 mL) at 0 °C over 90 min. The mixture was concentrated under vacuum and water (50 mL) was added to the residue. The aqueous phase was extracted with ether (3×50 mL), the combined organic phase was dried on $MgSO_4$, filtered and concentrated under vacuum, yielding 96% **5** (6.85 g, 38.4 mmol) as a clear oil. The spectroscopic data matched that reported.[12]

4.4. 4-(2-Bromo-5-methoxyphenyl)butyraldehyde (7)

Compound **6** (2.83 g, 6 mmol) was added to a solution of **5** (891 mg, 5 mmol) in DCM (50 mL). After 15 min, the mixture was poured in water (50 mL). The two phases were separated and the aqueous phase further extracted with DCM (50 mL). The combined organic phase was dried on $MgSO_4$, filtered, concentrated under vacuum and purified by column chromatography (silica, petroleum ether/ethyl acetate 5:1) yielding 84% **7** (1.08 g, 4.2 mmol) as a clear oil. The spectroscopic data matched that reported.[12]

4.5. 6-(2-Bromo-5-methoxyphenyl)hex-1-en-3-ol (9)

A solution of vinylmagnesium bromide in THF (1 M, 8.6 mL) was added to a solution of **7** (2.0 g, 7.78 mmol) in THF (78 mL) under nitrogen at rt (water bath). After 30 min, a saturated solution of NH_4Cl in water (80 mL) and ether (80 mL) were added. The two phases were separated and the aqueous phase was further extracted with ether (40 mL). The combined organic phase was dried on $MgSO_4$ and concentrated under vacuum yielding pure **9** quantitatively (2.23 g, 7.78 mmol) as a clear oil. R_f 0.30 (petroleum ether/ethyl acetate 3:1). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.37 (d, J=8.7 Hz, 1H, H-1), 6.74 (d, J=3.0 Hz, 1H, H-4), 6.60 (dd, J=8.7, 3.0 Hz, 1H, H-2), 5.85 (m, 1H, H-11), 5.20 (d, J=17.2 Hz, 1H, H-12 *trans* to H-11), 5.09 (d, J=10.4 Hz, 1H, H-12 *cis* to H-11), 4.11 (m, 1H, H-9), 3.75 (s, 3H, OMe), 2.69 (m, 2H, H-6), 1.71–1.57 (m, 5H, H-7 & H-8 & OH). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 158.9 (C-3), 142.5 (C-5), 141.0 (C-11), 133.2 (C-1), 116.0 (C-4), 114.8 (C-10), 114.9 (C-12), 113.0 (C-2), 73.0 (C-9), 55.4 (OMe), 36.5 (C-8), 36.1 (C-6), 25.7 (C-7). IR (neat, cm^{-1}): 3369 (s br), 2936 (m), 2963 (w), 1716 (w), 1594 (m), 1571 (m), 1471 (s), 1415 (m), 1277 (m), 1239 (s), 1191 (w), 1161 (m), 1136 (w), 1051 (m), 1013 (m), 990 (m), 922 (m), 868 (w), 852 (w), 799 (m), 688 (w).

4.6. 6-(2-Bromo-5-methoxyphenyl)-hex-1-en-3-one (10)

A turbid mixture of allylic alcohol **9** (860 mg, 3 mmol), iodobenzene diacetate (1.45 g, 4.5 mmol) and TEMPO (70 mg, 0.45 mmol) in DCM (3 mL) was stirred at rt under an atmosphere of air for 3 h. The mixture was diluted with DCM (15 mL), and a saturated solution of $Na_2S_2O_3$ in water (15 mL) and water (15 mL) were added. The two phases were separated and the aqueous phase was further extracted with DCM (2×15 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum and purified by column chromatography (silica, petroleum ether/ethyl acetate 9:1) yielding 82% **10** (693 mg, 2.45 mmol) as a clear oil. R_f 0.50 (petroleum ether/ethyl acetate 3:1). ^1H NMR (500 MHz, $CDCl_3$, δ): 7.38 (d, J=8.7 Hz, 1H, H-1), 6.75 (d, J=3.1 Hz, 1H, H-4), 6.61 (dd, J=8.7, 3.1 Hz, 1H, H-2), 6.34 (dd, J=17.7, 10.5 Hz, 1H, H-11), 6.19 (dd, J=17.7, 1.2 Hz, 1H, H-12 *trans* to H-11), 5.80 (dd, J=10.5, 1.2 Hz, 1H, H-12 *cis* to H-11), 3.76 (s, 3H, OMe), 2.72 (m, 2H, H-8), 2.63 (t, J=7.3 Hz, 2H, H-6), 1.95 (m, 2H, H-7). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 200.4 (C-

9), 158.9 (C-3), 141.9 (C-5), 136.5 (C-11), 133.3 (C-1), 128.1 (C-12), 116.0 (C-4), 114.9 (C-10), 113.4 (C-2), 55.4 (OMe), 38.7 (C-8), 35.4 (C-6), 23.9 (C-7).

4.7. 1-Bromo-4-methoxy-2-(4,4,6-trimethoxyhexyl)benzene (11)

A solution of **10** (493 mg, 1.74 mmol), trimethyl orthoformate (380 μL, 3.48 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (44 mg, 0.174 mmol) in methanol (8.7 mL) was heated to 70 °C under a nitrogen atmosphere. After 24 h, the mixture was extracted with ether (30 mL) and brine (30 mL). The organic phase was dried on $MgSO_4$, concentrated under vacuum and purified by column chromatography (silica, petroleum ether/diethyl ether 3:1) yielding 61% **11** (383 mg, 1.06 mmol) as a clear oil. R_f 0.25 (petroleum ether/diethyl ether 3:1) two elutions. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.38 (d, J=8.7 Hz, 1H, H-1), 6.75 (d, J=3.1 Hz, 1H, H-4), 6.60 (dd, J=8.7, 3.1 Hz, 1H, H-2), 3.76 (s, 3H, OMe on C-3), 3.32 (t, J=7.3 Hz, 2H, H-12), 3.28 (s, 3H, OMe on C-12), 3.12 (s, 6H, 2× OMe on C-9), 2.67 (m, 2H, H-6), 1.89 (t, J=7.3 Hz, 2H, H-11), 1.61 (m, 4H, H-7 & H-8). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 158.9, 142.3, 133.2, 116.1, 114.9, 113.1, 102.1 (C-9), 68.4 (C-12), 58.7 (OMe on C-12), 55.4 (OMe on C-3), 47.7 (2× OMe on C-9), 36.3 (C-8), 32.8 (C-6), 32.4 (C-11), 24.1 (C-7). IR (neat, cm^{-1}): 2952 (m), 2830 (w), 1595 (w), 1572 (m), 1471 (s), 1278 (m), 1239 (s), 1162 (m), 1107 (s), 1050 (s), 1013 (m), 961 (w), 903 (w), 870 (w), 851 (w), 800 (m). HRMS (positive FAB) calculated for $C_{16}H_{25}BrO_4$ (M+H): 361.10144, found 361.10194.

4.8. 4-Methoxy-1-methyl-2-(4,4,6-trimethoxyhexyl)benzene (12)

Trimethylboroxine (590 μL, 4.24 mmol) followed by K_3PO_4 (900 mg, 4.24 mmol) and $Pd(PPh_3)_4$ (122 mg, 0.106 mmol) were added to an emulsion of **11** (383 mg, 1.06 mmol) in water (4.25 mL) and methanol (4.25 mL) at rt. After 5 min, the mixture was heated to 90 °C for 24 h. The reaction was then quenched with brine (20 mL) and extracted with ether (3×20 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum and purified by column chromatography (silica, petroleum ether/diethyl ether 3:1) yielding 69% **12** (218 mg, 0.735 mmol) as a clear oil. R_f 0.38 (petroleum ether/diethyl ether 3:1) two elutions. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.01 (d, J=8.2 Hz, 1H, H-1), 6.69 (d, J=2.7 Hz, 1H, H-4), 6.63 (dd, J=8.2, 2.7 Hz, 1H, H-2), 3.75 (s, 3H, OMe on C-3), 3.30 (t, J=7.3 Hz, 2H, H-12), 3.27 (s, 3H, OMe on C-12), 3.11 (s, 6H, 2× OMe on C-9), 2.55 (m, 2H, H-6), 2.22 (s, 3H, Me-19), 1.89 (t, J=7.3 Hz, 2H, H-11), 1.58 (m, 4H, H-7 & H-8). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8 (C-3), 141.5 (C-5), 130.8 (C-1), 127.8 (C-10), 114.7 (C-4), 110.8 (C-2), 102.1 (C-9), 68.4 (C-12), 58.6 (OMe on C-12), 55.1 (OMe on C-3), 47.6 (2× OMe on C-9), 33.4 (C-8), 32.9 (C-6), 32.3 (C-11), 24.3 (C-7), 18.3 (C-19). IR (neat, cm^{-1}): 2949 (m), 2830 (w), 1609 (m), 1580 (w), 1500 (m), 1461 (m), 1251 (m), 1160 (m), 1108 (s), 1049 (s), 962 (w), 903 (m), 872 (w), 800 (m), 713 (w).

4.9. 1-Chloro-6-(5-methoxy-2-methyl-phenyl)-hexan-3-one (13)

A solution of HCl in water (6 M, 2 mL) was added to **12** (66 mg, 0.22 mmol) and the emulsion was stirred at 50 °C for 4 h. The mixture was then extracted with water (10 mL) and ether (2×10 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum and purified by column chromatography (silica, petroleum ether/diethyl ether 3:1) yielding 60% **13** (34 mg, 0.13 mmol) as a clear oil. R_f 0.32 (petroleum ether/diethyl ether 3:1) two elutions. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.03 (d, J=7.8 Hz, 1H, H-1), 6.66 (d, J=2.7 Hz, 1H, H-4), 6.65 (dd, J=7.8, 2.7 Hz, 1H, H-2), 3.80 (s, 3H, OMe), 3.72 (t, J=6.6 Hz, 2H, H-12), 2.85 (t, J=6.6 Hz, 2H, H-11), 2.56 (t, J=7.7 Hz, 2H, H-6), 2.48 (t, J=7.3 Hz, 2H, H-8), 2.21 (s, 3H, Me-19), 1.87 (m, 2H, H-7). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 207.1 (C-9), 157.8 (C-3), 140.8 (C-5), 131.0 (C-1), 128.0 (C-10), 114.8 (C-4), 111.0 (C-2), 55.2 (OMe), 45.0 (C-11), 42.6 (C-8), 38.3 (C-12), 32.6 (C-6), 23.6 (C-7), 18.3 (C-19).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.087. These data include MOL files and InChiKeys of the most important compounds described in this article.

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