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The Efficient and Enantiospecific Total Synthesis of Cyclopenta[*b*]phenanthrenes Structurally-related to Neurosteroids

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Abstract

We report an efficient synthesis of cyclopenta[*b*]phenanthrenes functionalized at C-3 and C-8 from an optically pure Hajos-Parrish ketone. The key step is a neutral alumina catalyzed Michael addition of a Hajos-Parrish ketone derivative (**4**) to 1,7-octadien-3-one (**2**) in 98% yield. This Michael addition product went through Krapcho decarbomethoxylation, aldol condensation, lithium liquid ammonia reduction, Wacker oxidation and acid catalyzed cyclization to form cyclopenta[*b*]phenanthrene (**1a**) in 37% overall yield for the 7 steps.

Keywords

cyclopenta[*b*]phenanthrenes; enantioselectivity; Hajos-Parrish ketone; Michael addition; total synthesis; steroids

Introduction

As part of our continuing interest in neurosteroid modulators of GABA_A receptors we reported two different synthetic routes to saturated cyclopenta[*b*]phenanthrenes functionalized at the C-3 and C-8 positions.¹ Neither of these synthetic routes was sufficiently robust to permit the preparation of adequate material for expansion of our initial GABA_A receptor structure–activity relationship (SAR) studies.² Additionally, we wanted to extend our SAR studies of neuroprotective estrogens³ to aromatic cyclopenta[*b*]phenanthrenes and also required an efficient route for their preparation. Previous routes are described in the literature for the preparation of racemic cyclopenta[*b*]phenanthrene analogues of 17β-estradiol.^{4–6} However, these synthetic routes, while adaptable to preparing optically pure compounds, are not optimal for our purposes. To achieve the goal of obtaining both saturated and aromatic cyclopenta[*b*]phenanthrenes in quantities suitable to be starting materials for both of our continuing SAR studies, we developed the following route.

Results and Discussion

Our retrosynthetic strategy is outline in Scheme 1. We planned to construct the A ring of compound **1a** from HCl catalyzed cyclization of diketone **8**. The B ring of compound **8** would be constructed from diketone **5** by sequential decarbomethoxylation, aldol

condensation and Wacker reaction of the terminal olefin. In turn, diketone **5** would come from the assembly of easily prepared carbomethoxylated enol **4** and 1,7-octadien-3-one (**2**).

Indenone **3** (prepared from optically pure Hajos–Parrish ketone as described previously),¹ was carbomethoxylated with dimethyl carbonate to give product **4** in 93% yield. 1,7-Octadien-3-one (**2**) was prepared in 70% overall yield by reaction of acrolin and Grignard reagent prepared from 5-bromo-1-pentene, followed by Jones oxidation.⁷

1,7-Octadien-3-one has been successfully used as a Michael acceptor in a reaction catalyzed by NaH for the total synthesis of (+)-19-nortestosterone.⁸ However, in our case the reaction of enol **4** and Michael acceptor **2** in the presence of NaH as described by that literature procedure, yielded only a complex mixture of non-Michael addition products and recovered enol **4** (43%). Hence, we searched for a neutral catalyst for the Michael addition. Ranu and Bhar have reported using neutral alumina as catalyst for Michael addition reactions of methyl vinyl ketone in high to quantitative yields.⁹ Using their methodology, we found that neutral alumina catalyzed the Michael addition of enol **4** to 1,7-octadien-3-one (**2**) to give routinely product **5** in 98% yield. The NMR spectrum of product **5** indicated that it was a 3:1 mixture of diastereomers resulting from the new chiral center formed in the reaction.

We initially attempted the decarbomethoxylation of compound **5** using NaI in refluxing HMPA and water (v/v = 2/1), no decarbomethoxylation product was formed and starting material was recovered.¹⁰ Subsequently, the decarbomethoxylation of indenone **5** was successfully carried out by the Krapcho reaction with LiCl in DMF.¹⁰ Part of the uncyclized decarbomethoxylation product cyclized to compound **6** during this reaction and these two products were not easily separated by column chromatography. Hence, we routinely removed the solvent under reduced pressure and used the crude product without further purification for an aldol condensation catalyzed by NaOH in EtOH to obtain cyclized compound **6** as the desired product in 75% overall yield for the 2 steps. When cyclization was attempted using pyrrolidine in CH₂Cl₂, no desired cyclization compound was formed and only starting material was recovered.¹¹ PTSA catalyzed cyclization in refluxing benzene was also tried.¹² No desired compound **6** was formed and the starting material was decomposed.

Although Michael addition product **5** was a 3:1 mixture of diastereomers, product **6** was not obtained as a mixture of diastereomers. When we tediously separated a small amount of the uncyclized product from the Krapcho reaction and examined it by ¹H and ¹³C NMR we found that this compound was a single stereoisomer. The involvement of an expected enol intermediate in the Krapcho reaction would allow the equilibration of the side chain to the thermodynamically more stable equatorial position and likely explains why product **6** is obtained as a single stereoisomer after the two step reaction sequence.

The enone **6** was reduced using lithium in liquid ammonia to afford compound **7** in 81% yield. As expected, lithium ammonia reduction of enone **6** gave exclusively the *trans* ring fusion product. The terminal olefin in benz[e]indene **7** was converted by Wacker oxidation to methyl ketone **8** in 77% yield.¹³ The diketone **8** was cyclized using 3 N HCl in MeOH to form cyclopenta[*b*]phenanthrenone **1a**. The ¹H NMR and ¹³C NMR as well as the optical rotation [α]_D²³ = - 32.6 (*c* = 0.35, CHCl₃) of cyclopenta[*b*]phenanthrenone **1a** are in good agreement with data we reported previously.¹ The stereochemistry of all chiral centers in compound **1a** was established previously by x-ray diffraction analysis of a compound derived from compound **1a**.²

Scheme 3 also shows the conversion of cyclopenta[*b*]phenanthrenone **1a** to **1b** and to the aromatic analogues **1c** and **1d**. Compound **1a** was oxidized by Jones reagent to form diketone **1b** in quantitative yield. Aromatic compound **1c** is obtained by aromatization of

compound **1b** by CuBr₂ and LiBr in 83% yield.¹⁴ Compound **1c** was reduced by NaBH₄ to give the 17 β -estradiol analogue **1d** in 93% yield.

Conclusions

We have developed a practical and highly efficient route to saturated and aromatic cyclopenta[*b*]phenanthrenes functionalized at the C-3 and C-8 positions. The key step of the synthetic route is the neutral alumina catalyzed Michael addition reaction of indenone derivative **4** with 1,7-octadien-3-one (**2**) in 98% yield. Preparation of compound **1a** has been achieved in 37% yield in 7 steps. This is an improvement over our previous synthetic routes which yielded product **1a** in yields of either 3.1% or 1.9%.

Experimental Section

General procedure

Except as otherwise indicated, all reactions were run under a nitrogen atmosphere in flame- or oven-dried glassware. Solvents were either used as purchased or dried and purified by standard methods. All extraction solvents were dried with anhydrous MgSO₄. Flash chromatography was performed using silica gel (particle size 32–63 μ m). Silica gel was supplied by Scientific Adsorbents Inc. Melting points were determined on a micro hot stage and are uncorrected. IR spectra were recorded as films on a KCl plate. NMR spectra were recorded at ambient temperature in CDCl₃ at 300 MHz (¹H) or 75 MHz (¹³C). Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26) for ¹H and chloroform (δ 77.0) for ¹³C. Reactions were monitored by thin layer chromatography (TLC) with 250 μ m pre-coated silica gel plates (Analtech). Yields refers to chromatographically and spectroscopically pure compounds unless otherwise noted. ¹H and ¹³C spectra were recorded on a Varian NMR spectrometer. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured on a Perkin Elmer Model 341 Polarimeter in the solvent indicated.

Synthesis of 1,7-Octadien-3-one (**2**)

A solution of 5-bromo-1-pentene (4.5 g, 30 mmol) in anhydrous EtOEt (20 mL) was added over 1 h to a stirred suspension of magnesium turnings (936 mg, 39 mmol) in EtOEt (20 mL). Freshly distilled acrolein (2.35 g, 42 mmol) was added to this mixture at –10 °C over 30 min. The mixture was stirred for an additional 30 min and quenched with aqueous NH₄Cl. The mixture was filtered through Celite® 545 and extracted with EtOEt (30 mL $\times$ 3), solvent was removed under reduce pressure. Without purification, the residue (3.85 g) was dissolved in acetone (20 mL) and Jones reagent was slowly added at 0 °C until a brown-yellowish color remained. The mixture was then quenched by added isopropanol (1 mL), brine (30 mL) was added and the solution was extracted with EtOEt (30 mL $\times$ 3). The solvent was removed and the residue was purified by flash chromatography (silica gel) with CH₂Cl₂ as eluent to afford 1,7-octadien-3-one (**2**, 2.86 g, 70%, two steps): ¹H NMR (CDCl₃) δ 6.40–6.18 (m, 2H), 5.85–5.72 (m, 2H), 5.06–4.96 (m, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.17 (dt, *J* = 19.5 Hz, 7.2 Hz, 2H), 1.79 (tt, *J* = 8.0 Hz, 7.2 Hz, 2H); ¹³C NMR (CDCl₃) δ 200.6, 137.9, 136.6, 127.8, 115.2, 38.7, 33.0, 22.9.

Synthesis of Carbomethoxylated Enol **4**

Dimethyl carbonate (2.70 g, 30 mmol) was added to a suspension of sodium hydride (0.8 g, 60% in mineral oil, 20 mmol) in THF (50 mL) at room temperature. The mixture was refluxed for 30 min. Then indenone **3** (2.24 g, 10 mmol) in THF (20 mL) was added by syringe. The reaction mixture was refluxed for 14 h and cooled down to room temperature. Acetic acid was slowly added to the mixture until pH 4–5 and water (50 mL) was added.

The products were isolated by extraction with EtOAc (100 mL $\times$ 3) and the combined extracts were dried. The solution was filtered and solvents were removed under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) to afford product **4** (2.62 g, 93%): ^1H NMR (CDCl_3) δ 12.30 (s, 1H), 3.75 (s, 3H), 3.58 (t, J = 7.6 Hz, 1H), 2.38-1.24 (m, 9H), 1.17 (s, 9H), 0.72 (s, 3H); ^{13}C NMR (CDCl_3) δ 173.7, 172.2, 96.8, 80.0, 72.4, 51.3, 41.5, 39.8, 35.0, 32.1, 31.4, 28.8, 25.6, 10.5.

Synthesis of Michael Additon Product 5

Neutral alumina (4.5 g) was heated at 180 $^\circ\text{C}$ under high vacuum for 4 h. After cooling down to room temperature, the flask was charged with N_2 . Compound **4** (2.54 g, 9 mmol), 1,7-octadien-3-one (**2**, 1.86 g, 15 mmol), and CH_2Cl_2 (20 mL) were added to the anhydrous alumina at room temperature. The mixture was stirred at room temperature for 16 h. The suspension was filtered through Celite[®] 545 and washed with CH_2Cl_2 (50 mL $\times$ 3). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to afford diastereomeric Michael addition product **5** (3.58 g, 98%). The major diastereomer had: ^1H NMR (CDCl_3) δ 5.71-5.62 (m, 1H), 4.94-4.86 (m, 2H), 3.62 (s, 3H), 3.35 (t, J = 7.1 Hz, 1H), 2.59-1.11 (m, 19H), 0.98 (s, 9H), 0.68 (s, 3H); ^{13}C NMR (CDCl_3) δ 209.5, 208.0, 173.7, 137.8, 115.0, 79.9, 72.4, 56.2, 52.2, 46.9, 45.5, 42.4, 42.1, 41.7, 38.1, 32.9, 31.3, 30.5, 28.6, 28.5, 25.5, 22.6; IR ν_{max} 2973, 1713, 1641, 1426, 1194, 1062 cm^{-1} ; Anal. Calcd for $\text{C}_{24}\text{H}_{38}\text{O}_5$: C, 70.90; H, 9.42; found: C, 70.67; H, 9.31.

Synthesis of Tricyclic Product 6

Lithium chloride (1.08 g, 25.5 mmol) was added to the Michael addition product **5** (3.45 g, 8.5 mmol) in anhydrous DMF (40 mL) at room temperature. The mixture was refluxed for 16 h and the solvent was removed under reduced pressure to afford the crude decarboxylation product. The crude product was dissolved in EtOH (30 mL) and 0.5 N NaOH (30 mL) was added at room temperature. The reaction mixture was refluxed and monitored by TLC. After 30 min, the starting material was completely consumed. The mixture was cooled to room temperature and quenched with aqueous NH_4Cl . The mixture was extracted with EtOAc (100 mL $\times$ 3) and dried. The solvent was filtered and removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to afford compound **6** (2.10 g, 75%, two steps) as a colorless oil: $[\alpha]_{\text{D}}^{25} = +72.8$ (c = 0.475, CHCl_3); ^1H NMR (CDCl_3) δ 5.77-5.68 (m, 1H), 4.94-4.83 (m, 2H), 3.37 (t, J = 8.8 Hz, 1H), 2.66-1.28 (m, 18H), 1.06 (s, 9H), 0.72 (s, 3H); ^{13}C NMR (CDCl_3) δ 198.9, 159.5, 138.2, 133.7, 114.4, 79.9, 72.2, 45.4, 44.5, 42.1, 37.5, 34.8, 33.4, 31.1, 30.9, 29.9, 28.6, 25.8, 24.4, 10.8; IR ν_{max} 2972, 1667, 1361, 1062 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{34}\text{O}_2$: C, 79.95; H, 10.37; found: C, 79.81; H, 10.44.

Synthesis of Compound 7

A three-neck flask fitted with a dry ice condenser was cooled to $-78\text{ }^\circ\text{C}$, and anhydrous ammonia (100 mL) was condensed into the flask. Lithium (0.57 g, 82 mmol, 10 equiv) was added, and the resulting blue solution was stirred for 0.5 h. To this was added a solution of compound **6** (2.0 g, 6.1 mmol) in dry THF (50 mL). After 3 h of stirring, solid NH_4Cl was added until the blue color disappeared, and the reaction mixture was allowed to warm to room temperature overnight and aqueous NH_4Cl was added. The mixture was extracted with EtOAc (100 mL $\times$ 3), and the combined organic fractions were washed with brine, dried and the solvent evaporated. Column chromatography (silica gel, 10% EtOAc in hexanes) gave compound **7** (1.63 g, 81%) as a white solid: $[\alpha]_{\text{D}}^{25} = +43.5$ (c = 0.98, CHCl_3); mp 72–73 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 5.82-5.69 (m, 1H), 4.98-4.88 (m, 2H), 3.38 (t, J = 7.2 Hz, 1H), 2.38-1.22 (m, 20H), 1.11 (s, 9H), 0.77 (s, 3H); ^{13}C NMR (CDCl_3) δ 212.1, 138.9, 114.3, 80.4, 72.1, 54.4, 48.5, 44.4, 44.2, 42.6, 42.1, 37.6, 34.3, 31.2 (2C), 30.4, 28.7, 25.7, 24.2,

11.8; IR ν_{max} 2973, 1712, 1461, 1196, 1065 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_2$: C, 79.46; H, 10.91; found: C, 79.66; H, 10.76.

Synthesis of Diketone 8

A suspension of PdCl_2 and CuCl were stirred in $\text{DMF}/\text{H}_2\text{O}$ (15 mL, $v/v = 9/1$) at room temperature under O_2 for 1 h. The terminal olefin **7** (1.61 g, 4.84 mmol) in $\text{DMF}/\text{H}_2\text{O}$ (10 mL, $v/v = 9/1$) was added by syringe. The reaction mixture was stirred and monitored by TLC. After 20 h, the starting material was completely consumed. The reaction was quenched with water (40 mL) and the products extracted with EtOAc (50 mL $\times$ 3), dried, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to give compound **8** (1.30 g, 77%) as a white solid: mp 64–66 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = +31.9$ ($c = 0.75$, CHCl_3); ^1H NMR (CDCl_3) δ 3.37 (t, $J = 7.2$ Hz, 1H), 2.47–2.11 (m, 5H), 2.09 (s, 3H), 1.87–1.09 (m, 15H), 1.06 (s, 9H), 0.72 (s, 3H); ^{13}C NMR (CDCl_3) δ 212.4, 208.9, 80.4, 72.1, 54.1, 48.5, 44.4, 44.2, 42.6, 42.1, 41.0, 37.6, 34.3, 31.2, 30.2, 29.8, 28.7, 25.6, 19.3, 11.7; IR ν_{max} 2972, 1713, 1361, 1196, 1066 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_3$: C, 75.82; H, 10.41; found: C, 75.95; H, 10.27.

Synthesis of 1a

To a solution of diketone **8** (1.28 g, 3.68 mmol) in MeOH (20 mL) was added 3 N HCl (20 mL) at room temperature. The reaction was stirred and refluxed for 16 h. After cooling to room temperature, the products were extracted with EtOAc (50 mL $\times$ 3), dried, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give compound **1a** (877 mg, 87%) as a white semisolid: $[\alpha]_{\text{D}}^{25} = -32.6$ ($c = 0.35$, CHCl_3); ^1H NMR (CDCl_3) δ 5.80 (s, 1H), 3.66 (t, $J = 8.0$ Hz, 1H), 2.46–2.01 (m, 7H), 1.54–0.80 (m, 14H), 0.77 (s, 3H); ^{13}C NMR (CDCl_3) δ 200.0, 167.0, 124.2, 81.2, 49.4, 44.6, 44.0, 42.8, 42.6, 37.1, 36.2, 35.7, 33.8, 30.1, 29.3, 25.9, 25.2, 11.1; IR ν_{max} 3430, 2913, 1670, 1043 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2$: C, 78.79; H, 9.55; found: C, 78.69; H, 9.44.

Synthesis of 1b

Jones reagent was added to a solution of compound **1a** (650 mg, 2.37 mmol) in acetone (40 mL) at 0 $^\circ\text{C}$ until a brown-yellowish color remained. After 10 min, the reaction was quenched by adding isopropanol (1.0 mL). Brine (50 mL) was added and the products were extracted with EtOAc (50 mL $\times$ 3), dried, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give compound **1b** (648 mg, 100%) as a white solid: mp 113–115 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = +30$ ($c = 0.45$, CHCl_3); ^1H NMR (CDCl_3) δ 5.78 (s, 1H), 2.45–0.90 (m, 20H), 0.88 (s, 3H); ^{13}C NMR (CDCl_3) δ 219.7, 199.3, 165.8, 124.5, 49.2, 47.4, 45.1, 42.4, 38.5, 36.9, 36.2, 35.5, 35.5, 33.4, 28.9, 26.0, 23.7, 13.4; IR ν_{max} cm^{-1} 2923, 1737, 1671, 1259; Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_2$: C, 79.37; H, 8.88; found: C, 79.47; H, 8.90.

Synthesis of 1c

To a solution of compound **1b** (450 mg, 1.65 mmol) in acetonitrile (20 mL) was added CuBr_2 and LiBr at room temperature. The mixture was stirred at room temperature and monitored by TLC. After 5 h, the starting material was completely consumed. The mixture was quenched with 3 N HCl (50 mL) and the products were extracted with EtOAc (50 mL $\times$ 3), dried, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give compound **1c** (371 mg, 83%) as a white solid: mp 260–262 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = +19.0$ ($c = 0.42$, DMSO); ^1H NMR ($\text{DMSO}-d_6$) δ 8.93 (s, 1H), 6.99 (d, $J = 7.7$ Hz, 1H), 6.46 (d, $J = 7.7$ Hz, 1H), 6.38 (s, 1H), 2.36–0.81 (m, 15H), 0.72 (s, 3H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 219.7, 155.8, 137.8, 130.7, 126.4, 115.6, 113.3, 48.0, 45.7, 44.2, 40.2,

39.5, 35.8, 31.1, 30.2, 29.8, 24.2, 13.9; IR $\nu_{\max}$ 3377, 1722, 1501, 1231 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_2$: C, 79.96; H, 8.20; found: C, 80.03; H, 7.98.

Synthesis of 1d

To a solution of compound **1c** (200 mg, 0.74 mmol) in EtOH (20 mL) was added NaBH_4 (75.6 mg, 2.0 mmol) at room temperature. After 1 h at room temperature, the starting material was completely consumed and the reaction was quenched with aqueous NH_4Cl and the products were extracted with EtOAc (50 mL $\times$ 3), dried, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to give compound **1d** (187 mg, 93%) as a white solid: mp 184–185 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = -44.1$ ($c = 0.34$, acetone); ^1H NMR (acetone- d_6) δ 7.93 (s, br, 1H), 7.04 (d, $J = 8.5$ Hz, 1H), 6.54 (dd, $J = 8.5$ Hz, 2.2 Hz, 1H), 6.46 (s, 1H), 3.61 (t, $J = 7.2$ Hz, 1H), 2.76–2.62 (m, 2H), 2.19–0.82 (m, 14H), 0.71 (s, 3H); ^{13}C NMR (acetone- d_6) δ 205.7, 155.3, 137.9, 131.6, 126.0, 115.2, 112.8, 81.0, 45.5, 45.0, 44.4, 43.4, 36.1, 31.4, 30.3, 30.1, 25.5, 11.1; IR $\nu_{\max}$ 3402, 1611, 1236, 1036 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_2$: C, 79.37; H, 8.88; found: C, 79.25; H, 8.67.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Retrosynthesis of compound **1a**.

Scheme 3.
Synthesis of A ring