Advanced Intramolecular Diels–Alder Study Toward the Synthesis of (–)-Morphine: Structure Correction of a Previously Reported Diels–Alder Product

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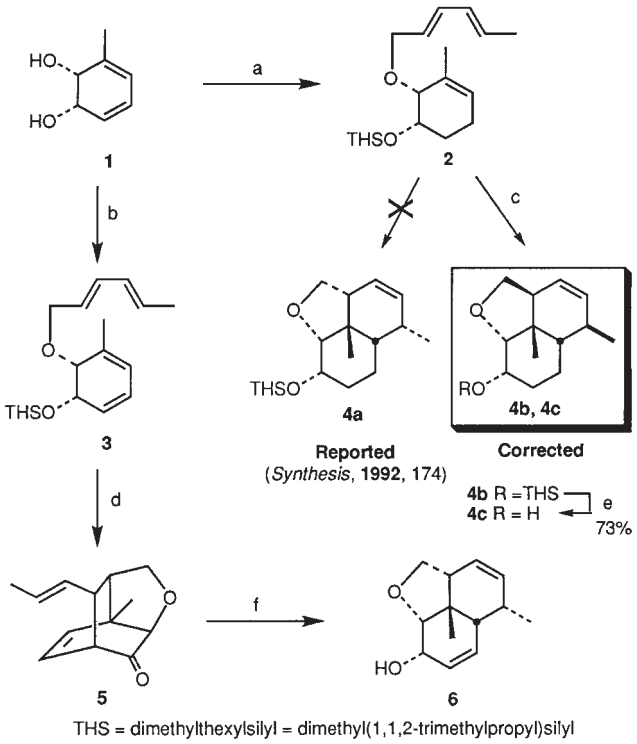
Abstract: A tricyclic ring system **18** containing all 5 chiral centers of the natural (–)-morphine skeleton has been synthesized in 9 steps. *cis*-Dienediol **11** was produced by a batch microbial dihydroxylation of (2-azidoethyl)benzene with the *E. coli* strain JM109(pDTG601). The key step in the synthesis was a thermal [4+2] intramolecular Diels–Alder cycloaddition of triene **16** which afforded the tricyclic adduct **17** in 62% yield. After deprotection, the absolute stereochemistry of the alcohol **18** was determined by X-ray crystallographic analysis. The previously reported Diels–Alder adduct **4a** was deprotected and the absolute stereochemistry of the free alcohol was assigned by X-ray crystallography to have the structure **4c**. This finding therefore constitutes the correction of the structure for **4a**.
Key words: chemoenzymatic synthesis, (–)-morphine, intramolecular Diels–Alder reaction, X-ray structure proof

Morphine (**7**), a potent analgesic and arguably the oldest drug in recorded history, has long been a challenging target for synthetic chemists. In spite of the previously reported 17 total or formal syntheses of morphine,[1–17] a truly practical synthesis, which would rival the economy of isolation from natural opium, continues to elude the synthetic community. Although none of the total or formal syntheses of morphine relied on a [4+2] cycloaddition as the pivotal step, several successful attempts at morphinan syntheses utilizing intramolecular Diels–Alder methodology have been published.[18–22]

In 1992, we published a model study[23] that employed a Diels–Alder cyclization or a Diels–Alder and Cope rearrangement sequence to obtain tricycles **4a** and **6** respectively (Scheme 1). The stereochemistry of **4a** and **6** was deduced from NOE correlations, but the two structures have not been converted to a common intermediate for unambiguous comparison. In this paper, we report an advanced Diels–Alder study and concomitant correction of the structure **4a** to that of **4b** via its free alcohol **4c.**

On the assumption that the tricycle **4a** was produced stereoselectively via the *endo* transition state (Scheme 1), we turned to the advanced model study in which a leaving group at the incipient C_9 of morphine **7** would be displaced by a nucleophilic nitrogen at C_{16} to form the bridged product **8** (Figure). Before committing to the halide **9b** or tosylate **9c**, we set out to synthesize model compound **9a** by analogous Diels–Alder methodology. The methyl-substituted diene provided the simplest model for establishing the stereochemical outcome of the cycloaddition of a terminally functionalized diene ether.

Whole cell biooxidation of (2-azidoethyl)benzene (**10b**), easily synthesized from commercially available (2-bromoethyl)benzene (**10a**), readily afforded *cis*-dienedio] **11** stereospecifically and in good yield of approximately 6 g/L[24] (Scheme 2). Reduction of the less substituted olefin with diimide (generated from potassium azodicarboxylate) afforded diol **12**. Alternatively, diol **12** was obtained in a more laborious procedure by microbial dihydroxylation of (2-bromoethyl)benzene (**10a**) (10 g/L),[25] followed by diimide reduction, and protection as the acetonide. Displacement of the bromide with sodium azide followed by acetonide cleavage afforded free diol **12.**[24] Selective protection of the homoallylic hydroxy group yielded silyl ether **13**. Alkylation of the allylic oxygen upon exposure of its sodium alkoxide to sorbyl bromide[26] gave triene **14.** The azide was reduced to amine **15** and converted to acet-



Scheme 1

a: (i) potassium azodicarboxylate (PAD), HOAc, MeOH; (ii) THS-Cl, imidazole, DMF; (iii) NaH, sorbyl bromide, THF. **b**: (i) THS-Cl, imidazole, DMF; (ii) NaH, sorbyl bromide, THF. **c**: toluene, sealed tube. 210°C, 24 h. **d**: (i) CCl_4, reflux, 7 h; (ii) $Bu_4NF{\cdot}3\ H_2O$, THF, r.t., 24 h; (iii) PCC, CH_2Cl_2, r.t., 24 h. **e**: HF/MeCN (5:95), 12 h. **f**: (i) xylenes, sealed tube, 250°C; (ii) $NaBH_4$, $CeCl_3{\cdot}7\ H_2O$, MeOH, r.t., 15 min.

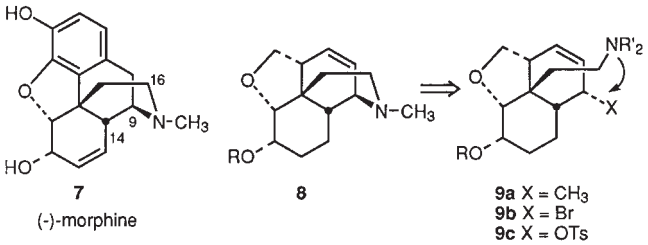
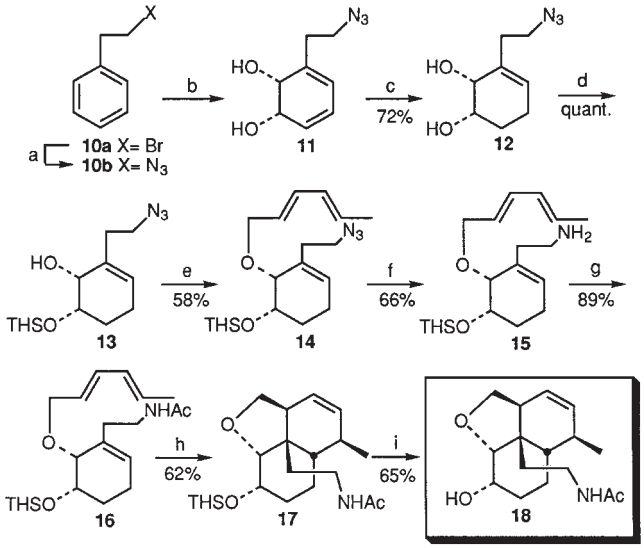


Figure. Retrosynthetic Analysis

amide **16**. The resulting triene **16** was cyclized under conditions similar to those by which **4a** was prepared[23] to afford the cycloadduct **17** as a single stereoisomer in 62% yield. Since an unambiguous assignment of the absolute stereochemistry by spectroscopy was not possible, a single crystal of the alcohol **18**, obtained by deprotection of tricycle **17**, was grown. X-ray crystallographic analysis confirmed the stereochemistry of the cycloadduct **18** as shown[27] and indicated that the [4+2] cycloaddition proceeded via an *exo* transition state.



Scheme 2

a: NaN_3, DMF. **b**: *E. coli* JM109(pDTG601). **c**: PAD, HOAc, MeOH, 0°C–r.t., 14 h. **d**: THSCl, imidazole, DMF, 0°C, 13 h. **e**: NaH, sorbyl bromide, THF, 0 °C-r.t., 14 h. **f**: PPh_3. 0.4% H_2O/THF, 45 °C 18 h. **g**: Ac_2O, pyridine, r.t., 2 h. h: toluene, sealed tube, 230°C, 20 h. **i**: HF/MeCN (5:95), r.t., 3.5 h.

On the basis of this observation, we reinvestigated the stereochemical assignment of the reported *endo* cycloadduct **4a** by X-ray crystallography of its free alcohol and confirmed this structure as **4c**,[28] therefore proving that the intramolecular Diels–Alder reaction proceeded in an *exo* fashion to afford both **18** and **4c**. This result serves as a formal structure correction of cycloadduct **4a**.

The combination of enzymatic chemistry and a stereospecific intramolecular Diels–Alder reaction allowed for the efficient synthesis of tricycle **18**, which contains all of the stereocenters of natural (–)-morphine in the correct absolute configuration. It is noteworthy that the intramolecular Diels–Alder cyclization led to the correct stereochemistry of both C_{14} and C_9 of morphine, a feat not simultaneously attained by most of the previously reported strategies.

In light of the stereochemical outcome of the Diels–Alder reaction, it is clear that our next strategy must focus on a flexible approach to accommodate the *exo* versus *endo* options in the [4+2] cycloaddition. If the *E,E*-dienes continue to produce the β-C_9 stereochemistry via the *exo* transition state in the thermal cycloaddition, then C_9 will need to contain a nucleophilic nitrogen while a leaving group will be installed at C_{16} (see numbering in morphine **7**) that is on the ethyl side chain of diols such as **11**. Several such compounds (X=OH, OAc, etc.) have recently become available.[24] For possible *endo* transition states, the placement of leaving groups and nucleophiles will be switched between C_9 and C_{16}. Finally, the use of *E,Z*-dienes equipped with terminal leaving groups (Cl, OTs, etc.) would provide additional flexibility in controlling the stereochemistry for the nucleophilic displacement and construction of the bridge. The preparation of compounds of type **9b** via cycloadditions of *E,Z*-halodienes is currently under way and will be reported in due course.

All non-hydrolytic reactions were performed in solvents either dried according to standard procedures or purchased from Aldrich. Analytical TLC was performed on silica gel 60F-254 (Whatman). Flash chromatograaphy was performed on Fisher silica gel (grade 60, 200–425 mesh). ^{1}H NMR spectra were recorded on a Varian VXR-300 and ^{13}C multiplicities were determined by APT experiments. MS were recorded on a Finnigan Mat 95 Q mass spectrometer. IR spectra were obtained on a Perkin Elmer 1600 Series instrument. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Mps were obtained on a Thomas Hoover Uni-melt apparatus.

(2a*S*,5*R*,5a*S*,8*S*,8a*R*,8b*S*)-5,8b-Dimethyl-2a,5,5a,6,7,8,8a,8b-octahydro-2*H*-benzo[*cd*]isobenzofuran-8-ol (4c):

To a solution of tricyclic silyl ether **4b** (74 mg, 0.24 mmol) in MeCN (9.5 mL) was added 48% aq HF (0.5 mL). The reaction mixture was stirred for 12 h at r.t. Water (40 mL) was added, the aqueous phase was neutralized with 10% NaOH and extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). After concentration by rotary evaporation, the crude product was purified by flash column chromatography (4:1 hexanes/EtOAc) to afford the tricyclic alcohol **4c** (32 mg, 73%) as a colorless, viscous oil which crystallized from $CDCl_3$ by slow evaporation to obtain single crystals for X-ray analysis; R_f = 0.20 (4:1 hexanes/EtOAc).
IR ($CHCl_3$): ν = 3420, 3020, 2960, 2930, 2870, 1210 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.63 (dt, J = 9.5, 2.2 Hz, 1H), 5.56 (dt, J = 9.5, 2.2 Hz, 1H), 4.12 (t, J = 7.6 Hz, 1H), 3.90 (m, 1H), 3.64 (m, 2H), 3.02 (m, 1H), 2.51 (s, 1H), 1.90 (m, 2H), 1.62 (m, 1H), 1.38 (m, 3H), 1.12 (d, J = 7.6 Hz, 3H), 0.88 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0 (CH), 122.3 (CH), 84.2 (CH), 69.6 (CH_2), 66.4 (CH), 47.7 (CH), 42.9 (CH_2), 39.6 (CH_3), 37.3 (CH_3), 28.5 (CH_2), 23.2 (CH), 23.= (CH), 22.7 (CH_2).
HRMS: 209.1504 ($C_{13}H_{20}O_2$+H) requires 209.1541.

(1*S*,2*R*)-3-(2-Azidoethyl)cyclohex-3-ene-1,2-diol (12):

To a solution of azidodienediol **11** (~35 g, 0.19 mol) in MeOH (300 mL) was added potassium azodicarboxylate (PAD, 85 g, 0.44 mol). The suspension was cooled to 0 °C, and a mixture of HOAc (50 mL) and MeOH (100 mL) was added dropwise over 2 h. The solution was allowed to warm to r.t. and continued stirring for 14 h. Additional HOAc (10 mL) was added to decompose any excess PAD, and the mixture was concentrated by rotary evaporation. Water (150 mL) was added and the crude product was extracted into CH_2Cl_2 (5 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The remaining solid was recrystallized (CH_2Cl_2/hexanes) to afford diol **12** (25 g, 72%) as a white crystalline material; mp 54–55 °C; R_f = 0.13 (1:1, hexane/EtOAc); $[\alpha]_D^{29}$ –98.5 (c = 1.0, $CHCl_3$).

Anal. Found: C, 52.47; H, 7.09; N, 22.78. $C_8H_{13}O_2N_3$ requires: C, 52.43; H, 7.16; N, 22.94.
IR (KBr): ν = 3280, 2940, 2095, 1260, 1080 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.66 (bs, 1H), 3.99 (d, J = 3.4 Hz, 1H), 3.75 (m, 1H), 3.40 (t, J = 7 Hz, 2H), 2.96 (s, 2H), 2.40 (m, 2H), 2.16 (m, 1H), 2.08 (m, 1H), 1.70 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.9 (C), 128.1 (CH), 69.5 (CH), 68.6 (CH), 50.1 (CH_2), 34.0 (CH_2), 25.1 (CH_2), 23.9 (CH_2).
MS (EI): m/z (%) = 184 (M^+, 8), 138 (42), 120 (100).
HRMS: 184.1153, ($C_8H_{13}O_2N_3$+H) requires 184.1086.

(1*R*,6*S*)-2-(2-Azidoethyl)-6-(dimethylthexylsiloxy)cyclohex-2-en-1-ol (13):
To a cooled (0°C) solution of diol **12** (122 mg, 0.67 mmol) in DMF (0.75 mL) was added imidazole (54 mg, 0.80 mmol) followed by THS-Cl (142 mg, 0.80 mmol). The mixture was stirred briefly and allowed to stand at 0 °C for 13 h. Water (40 mL) was added and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (9:1 hexane/EtOAc) to afford **13** (214 mg, 99%) as a colorless oil; R_f = 0.49 (9:1 hexane/EtOAc); $[\alpha]_D^{26}$ –37.0 (*c* = 1.2, $CHCl_3$).
Anal. Found: C, 59.11; H, 9.64; N, 12.84. $C_{16}H_{31}O_2N_3Si$ requires: C, 59.04; H, 9.60; N, 12.91.
IR ($CHCl_3$): ν = 3550, 2950, 2095, 1460, 1370, 1250, 1080 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ = 5.65 (bs, 1H), 3.89 (bs, 1H), 3.81 (dt, *J* = 10.7, 3.9 Hz, 1H), 3.41 (m, 2H), 2.66 (d, *J* = 2.7 Hz, 1H), 2.42 (m, 2H), 2.17 (m, 1H), 2.02 (m, 1H), 1.77 (m, 1H), 1.63 (sept, *J* = 6.9 Hz, 1H), 1.55 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 6H), 0.14 (s, 3H), 0.13 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.7 (C), 127.6 (CH), 70.8 (CH), 68.8 (CH), 50.0 (CH_2), 34.5 (CH_2), 34.2 (CH), 25.3 (CH_2), 24.9 (C), 24.1 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), –2.4 (CH_3), –3.0 (CH_3).
MS (EI) *m/z* (%) = 308 (M-H_2O^+, 45), 280 (100).

(5*S*,6*R*)-1-(2-Azidoethyl)-5-(dimethylthexylsiloxy)-6-[(2*E*,4*E*)-hexa-2,4-dienyloxy]cyclohex-1-ene (14):
To a cooled (0°C) suspension of 60% NaH in mineral oil (117 mg, 2.92 mmol) in THF (1 mL) was added dropwise a solution of the mono protected azide **13** (476 mg, 1.46 mmol) in THF (2 mL). The mixture stirred at 0°C for 20 min. A solution of sorbyl bromide (353 mg, 2.19 mmol) in THF (1 mL) was added dropwise. The cooling bath was removed and the mixture was stirred for 14 h. Water (70 mL) was added and the crude product was extracted into Et_2O (3 × 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a crude product which was purified by repeated column chromatography (99:1 hexane/EtOAc) [*note*: 3 separate columns were necessary to separate the product from unreacted sorbyl bromide] to afford **14** as a pale yellow oil (344 mg, 58%); R_f = 0.61 (95:5 hexane/EtOAc); $[\alpha]_D^{26}$ –53.2 (*c* = 1.11, $CHCl_3$).
IR ($CHCl_3$): ν = 2950, 2870, 2095, 1460, 1380, 1250, 1100 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ = 6.17 (dd, *J* = 14.8, 10.2 Hz, 1H), 6.05 (ddd, *J* = 14.7, 10.4, 1.7 Hz, 1H), 5.68 (m, 2H), 5.55 (bs, 1H), 4.46 (dd, *J* = 12.1, 5.8 Hz, 1H), 4.09 (dd, *J* = 12.1, 7.1 Hz, 1H), 3.82 (dt, *J* = 11.0, 3.0 Hz, 1H), 3.64 (d, *J* = 3.0 Hz, 1H), 3.33 (m, 2H), 2.34 (m, 2H), 2. 18 (m, 1H), 2.03 (m, 1H), 1.90 (m, 1H), 1.75 (d, *J* = 6.6 Hz, 3H), 1.66 (sept, *J* = 6.8 Hz, 1H), 1.58 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.85 (s, 3H), 0.12 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.5 (C), 133.0 (CH), 130.9 (CH), 129.8 (CH), 127.7 (CH), 127.3 (CH), 76.9 (CH), 73.0 (CH_2), 71.9 (CH), 50.2 (CH_2), 34.1 (CH_2), 34.0 (CH_3), 25.7 (CH_2), 24.9 (C), 24.8 (CH_2), 20.3 (2 x CH_3), 18.6 (CH_3), 18.1 (CH_3), –2.6 (2 × CH_3).
HRMS: 406.2824, ($C_{22}H_{39}O_2N_3Si$+H) requires 406.2889.

(5*S*,6*R*)-1-(2-Aminoethyl)-5-(dimethylthexylsiloxy)-6-[(2*E*,4*E*)-hexa-2,4-dienyloxy]cyclohex-1-ene (15):
To a solution of azide **14** (106 mg, 0.26 mmol) in THF (10 mL) was added PPh_3(102.8 mg, 0.39 mmol) and water (0.04 mL). After stirring at 45 °C for 18 h, the mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (EtOAc-50% saturated with NH_4OH) [*note*: The eluent was prepared by diluting EtOAc fully saturated with NH_4OH with an equal volume of 100% EtOAc] to afford the amine **15** as a pale yellow oil (65 mg, 66%); R_f = 0.71 (7:3: 1 EtOAc/ EtOH/NH_4OH); $[\alpha]_D^{28}$ –72.5 (*c* = 1.22, $CHCl_3$).
IR ($CHCl_3$): ν = 3020, 2960, 2870, 1220, 1090 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ = 6.15 (dd, *J* = 14.9, 10.5 Hz, 1H), 6.05 (ddd, *J* = 14.4, 9.0, 1.5 Hz, 1H), 5.66 (m, 2H), 5.46 (s, 1H), 4.46 (dd, *J* = 12.5, 6.1 Hz, 1H), 4.08 (dd, *J* = 11.7, 6.8 Hz, 1H), 3.78 (dt, *J* = 11.2, 3.2 Hz, 1H), 3.58 (d, *J* = 2.7 Hz, 1H), 2.76 (m, 2H), 2.18 (m, 2H), 2.02 (m, 1H), 1.94 (m, 1H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.66 (sept, *J* = 6.8 Hz, 1H), 1.57 (m, 1H), 1.38 (bs, 2H), 0.90 (s, 3H), 0.88 (s, 3H), 0.84 (s, 6H), 0.12 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.7 (C), 132.7 (CH), 130.9 (CH), 129.5 (CH), 128.0 (CH), 126.3 (CH), 77.3 (CH), 73.2 (CH_2), 72.6 (CH), 40.4 (CH_2), 39.2 (CH_2), 34.0 (CH_3), 25.6 (CH_2), 25.0 (C), 24.9 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), –2.6 (2 × CH_3).
HRMS: 380.2977, ($C_{22}H_{41}O_2NSi$+H) requires 380.2984.

(5*S*,6*R*)-1-(2-Acetamidoethyl)-5-(dimethylthexylsiloxy)-6-[(2*E*,4*E*)-hexa-2,4-dienyloxy]cyclohex-1-ene (16):
To a solution of amine **15** (263 mg, 0.69 mmol) in pyridine (2 mL) was added Ac^2O (106 mg, 1.04 mmol), and the mixture was stirred at r.t. for 2 h. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (100% EtOAc) to afford the amide **16** (259 mg, 89%) as a colorless, viscous oil; R_f = 0.69 (EtOAc fully saturated with NH_4OH); $[\alpha]_D^{28}$ –78.9 (*c* = 1.15, $CHCl_3$).
IR ($CHCl_3$): ν = 3450, 3020, 2980, 2900, 1660, 1520, 1220, 1050 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ = 6.18 (dd, *J* = 14.8, 10.2 Hz, 1H), 6.03 (ddd, *J* = 14.8, 10.4, 1.7 Hz, 1H), 5.67 (m, 2H), 5.51 (bs, 1H), 4.52 (dd, *J* = 11.8, 6.0 Hz, 1H), 4.05 (dd, *J* = 11.8, 7.0 Hz, 1H), 3.83 (dt, *J* = 10.7, 3.3 Hz, 1H), 3.61 (d, *J* = 2.8 Hz, 1H), 3.31 (m, 2H), 2.32 (m, 1H), 2.10 (m, 3H), 1.92 (m, 1H), 1.89 (s, 3H), 1.74 (d, *J* = 6.9 Hz, 3H), 1.64 (sept, *J* = 6.9 Hz, 1H), 1.56 (m, 1H), 0.89 (s, 3H), 0,88 (s, 3H), 0.84 (s, 6H), 0.12 (s, 3H), 0.11 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0 (C), 134.1 (C), 133.4 (CH), 130.8 (CH), 130.2 (CH), 127.4 (CH), 127.2 (CH), 77.9 (CH), 73.0 (CH_2), 71.9 (CH), 38.7 (CH_2), 34.3 (CH_2), 34.0 (CH_3), 25.8 (CH_2), 24.9 (C), 24.7 (CH_2), 23.3 (CH), 20.4 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), –2.6 (2 × CH_3).
MS (FAB): *m/z* (%) = 422 (M+H^+, 4), 324 (86), 265 (98).
HRMS: 422.3056, ($C_{24}H_{43}O_3NSi$+H) requires 422.3090.

(2a*S*,5*R*,5a*S*,8*S*,8a*R*,8b*S*)-8b-(2-Acetamidoethyl)-8-(dimethylthexylsiloxy)-5-methyl-2a,5,5a,6,7,8,8a,8b-octahydro-2*H*-benzo[*cd*]isobenzofuran (17):
A solution of triene **16** (126 mg, 0.299 mmol) in toluene (15 mL) was placed in a thick-wall glass reaction tube equipped with a Teflon screw cap. The reaction mixture was degassed using 3 repeated freeze-pump-thaw cycles, lowering the reaction tube's temperature to –78 °C at the start of each cycle, and sealed under argon. The reaction tube was placed in a sand bath preheated to 230 °C. After 20 h, the tube was cooled in a liquid nitrogen bath, carefully opened, and the contents removed. The toluene was distilled off under reduced pressure, and the crude product was purified by column chromatography (100% EtOAc) to afford the tricycle **17** (78 mg, 62%) as a colorless oil. Crystallization from hexanes afforded colorless crystals; mp 123–124°C; R_f = 0.21 (100% EtOAc); $[\alpha]_D^{26}$ +11.0 (*c* = 1.0, $CHCl_3$).
Anal. Found: C, 67.85; H, 10.03; N, 3.24. ($C_{24}H_{43}NO_3Si$) requires: C, 68.36; H, 10.28; N, 3.32. (Best result obtained after repeated analyses of recrystallized product.)
IR (KBr): ν = 3240, 2960, 2860, 1640, 1560, 1440, 1380, 1250, 1080 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ = 5.64 (dt, *J* = 9.6, 2.8 Hz, 1H), 5.57 (dt, *J* = 9.6, 2.8 Hz, 1H), 5.44 (bs, 1H), 4.10 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.95 (t, *J* = 3.6 Hz, 1H), 3.71 (d, *J* = 5.2 Hz, 1H), 3.54 (dd, *J* = 11.5, 6.9 Hz, 1H), 3.42 (m, 1H), 3.29 (m, 1H), 3.12 (m, 1H), 1.94 (s, 3H), 1.90 (m, 1H), 1.64 (m, 5H), 1.44 (m, 1H), 1.27 (m, 2H), 1.14 (d, *J* = 7.7 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 6H), 0.83 (s, 6H), 0.12 (s, 3H), 0.08 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C), 135.1 (CH), 123.2 (CH), 79.8 (CH), 68.6 (CH_2), 68.1 (CH), 45.9 (C), 42.7 (CH), 40.0 (CH), 37.4 (CH), 35.8 (CH_2), 34.0 (CH), 31.4 (CH_2), 30.1 (CH_2), 24.8 (C), 23.3 (CH_3), 23.0 (CH_3), 22.9 (CH_2), 20.2 (2 × CH_3), 19.0 (CH_3), 18.5 (CH_3), –2.6 (CH_3), –3.2 (CH_3).
MS (FAB) *m/z* = 422 (M+H)$^+$.
HRMS: 422.3056, ($C_{24}H_{43}O_3NSi$+H) requires, 422.3090.

(2a*S*,5*R*,5a*S*,8*S*,8a*R*,8b*S*)-8b-(2-Acetamidoethyl)-5-methyl-2a,5,5a,6,7,8,8a,8b-octahydro-2*H*-benzo[*cd*]isobenzofuran-8-ol (18):

To a solution of tricycle **17** (90 mg, 0.21 mmol) in MeCN (9.5 mL) was added 45% aq HF (0.5 mL). The mixture was stirred at r.t. for 1.5 h and another portion of 45% aq HF (0.5 mL) was added. After stirring an additional 2 h, the mixture was neutralized with 10% NaOH and extracted with Et_2O (3 × 10 mL), The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (95:5 EtOAc/MeOH) to obtain the alcohol **18** (24 mg, 65%) as a colorless, viscous oil. Crystallization from $CDCl_3$ (the solution was allowed to evaporate slowly from a capped tube at r.t. over several weeks) afforded single crystals suitable for X-ray analysis; mp 186–188 °C; R_f = 0.21 (95:5 EtOAc/MeOH); $[\alpha]_D^{29}$ +5.75 (*c* = 0.4, $CHCl_3$).

Anal. Found: C, 68.59; H, 8.98, N, 5.03. ($C_{16}H_{25}NO_3$) requires C, 68.79; H, 9.02; N, 5.01.

IR (neat) ν = 3680, 3020, 2980, 1730, 1670, 1520, 1420, 1210, 1050 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.60 (bs, 1H), 5.49 (bs, 1H), 4.15 (t, *J* = 8.3 Hz, 1H), 3.94 (m, 1H), 3.85 (d, *J* = 5.6 Hz, 1H), 3.63 (dd, *J* = 12.0, 7.6, Hz, 1H), 3.41 (m, 1H), 3.18 (m, 2H), 2.21 (bs, 1H), 1.94 (s, 3H), 1.90 (bs, 1H), 1.68 (m, 3H), 1.43 (m, 1H), 1.26 (m, 3H), 1.15 (d, *J* = 7.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0 (C), 135.5 (CH), 122.0 (CH), 80.2 (CH), 69.2 (C), 66.5 (CH), 45.5 (C), 42.4 (CH), 40.6 (CH), 37.4 (CH), 35.8 (CH_2), 31.2 (CH_2), 28.3 (CH_2), 23.3 (CH_3), 22.9 (CH_3), 22.6 (CH_2).

MS (CI/methane): *m/z* (%) = 280 ($M+H^+$, 100), 262 (35).

HRMS: 280.1959, ($C_{16}H_{25}NO_3$+H) requires 280.1912.

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(27) X-ray data for 18: $C_{16}H_{25}NO_3$, M_r = 279.37, Orthorhombic, $P2_12_12_1$, a = 7.6014(1) Å, b = 10.6199(3) Å, c = 18.8051(6) Å, V = 1518.06(7) $Å_3$, Z = 4, $D_{calc.}$ = 1.222 g cm^{-3}, Mo Kα (λ = 0.71073 A), T = 173 K. The structure was solved by the Direct Methods in *SHELXTL5*, and refined using full-matrix least squares. The non-H atoms were treated anisotropically. The hydrogen atoms were obtained from a Diffference Fourier map and refined without constraints. 282 parameters were refined in the final cycle of refinement using 2530 reflections with I > 2σ(I) to yield R_1 and wR_2 of 3.87 and 7.41%, respectively. Refinement was done using F^2.
(28) X-ray data for 4c: $C_{13}H_{20}O_2$, M_r = 208.29, Orthorhombic, $P2_12_12_1$, a = 6.2053(2) Å, b = 1386542(1) Å, c = 13.8944(4) Å, V = 1177.25(5) $Å^3$, Z = 4, $D_{calc.}$ = 1.175 g cm^{-3}, Mo Kα (λ = 0.71073 Å), T = 173 K. The structure was solved by the Direct Methods in *SHELXTL5*, and refined using full-matrix least squares. The non-H atoms were treated anisotropically. The hydrogen atoms were obtained from a Diffference Fourier map and refined without constraints. 217 parameters were refined in the final cycle of refinement using 2236 reflections with I > 2σ(I) to yield R_1 and wR_2 of 4.26 and 9.15%, respectively. Refinement was done using F^2.
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