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A model study for the total synthesis of (±)-scopadulin: stereoselective construction of the A/B ring system with desired functionalities

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Abstract—A model study toward the total synthesis of (±)-scopadulin is described. Stereocontrolled synthesis of the A/B ring system with desired functionalities was achieved by stereoselective cyanation of a bicyclic enone with Et_2AlCN, diastereoselective construction of a quaternary carbon at C-4 with LDA-BOMCl, and conversion of the cyano group into a methyl group.

1. Introduction

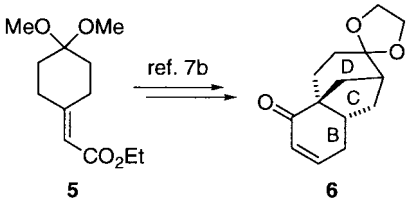
The plant *Scoparia dulcis* has long been used as a traditional medicine in Paraguay, India and Taiwan for hypertension and stomach disorders.[1] Several scopadulane diterpenes such as scopadulcic acid A (**1**), scopadulcic acid B (**2**) were isolated from this plant by T. Hayashi and co-workers.[2] The continued investigation of Hayashi's group on this plant resulted in isolation and characterization of a novel tetracyclic diterpenoid, scopadulin (**3**), in 1990.[3] This is the first example of an aphidicolane type diterpenoid from a higher plant. The structure of scopadulin was determined by spectroscopic studies, and finally confirmed by a single crystal X-ray crystallography of its acetone solvate[3] (Fig. 1).

The challenging structural complexity of scopadulin due to the presence of three quaternary carbons and eight stereocenters coupled with its notable antiviral and cytotoxic activities[3] makes it a worthy synthetic target. Although synthetic pathways of scopadulcic acid A (**1**)[4] and scopadulcic acid B (**2**)[4b,5] have been established in recent years, no synthetic approach towards scopadulin (**3**) is reported to date.[6] After a successful synthesis of aphidicolin,[7] we were inspired to synthesize this novel diterpenoid. However, progress of our synthetic study was hampered due to several failed attempts to construct the A/B ring system with desired functionalities. Accordingly, we turned our attention to the synthesis of a model compound **4**, which bears the same functionalities and stereochemical configuration as those of scopadulin (**3**). Herein we wish to report the synthetic studies of model compound **4** in full detail.[8]

2. Results and discussion

2.1. Stereoselective construction of A/B-ring system with a quaternary carbon center at C-4

We had already established a synthetic pathway of the intermediate **6** (Eq (1)),[7b] which could be as a key intermediate for the synthesis of scopadulin. Therefore, cyclohex-2-en-1-one **7** was taken as the starting material for our model study. We initially planned to synthesize the model compound **4** via a bicyclic enone **11** bearing a methyl substituent at C-4 (Scheme 1).[†]



5 **6** (1)

The enone **11** was synthesized in a straightforward manner as depicted in Scheme 1. Barbier alkylation of **7** provided

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† For convenience of description, the numbering of carbons of the compounds **4**, **11**, **15**, **16**, **20**–**22**, **24**–**26**, **28**, and **30** (Fig. 1, Schemes 1–6) was that used for scopadulin (**3**).

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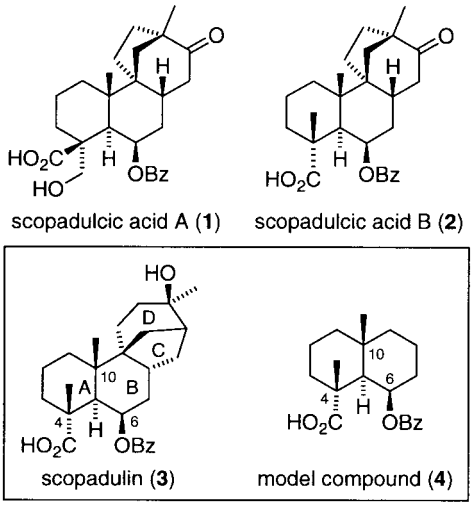
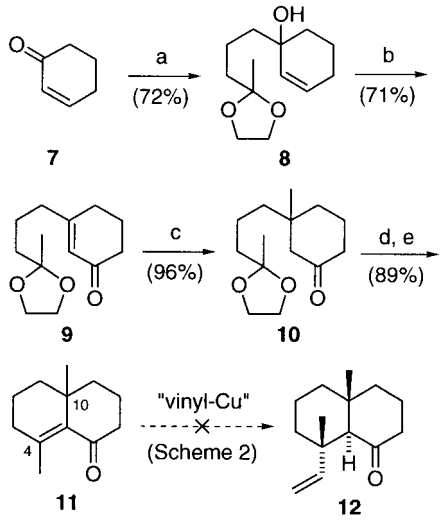


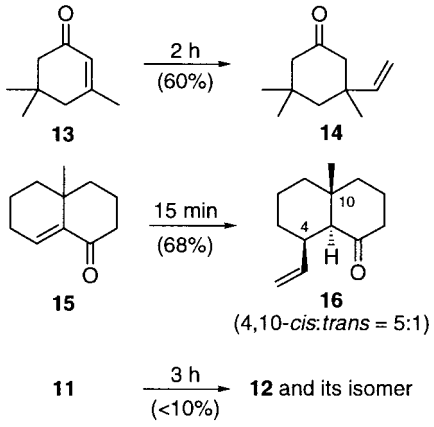
Figure 1.

the allyl alcohol **8**, which was oxidized to give the enone **9**, both in good yields. Conjugate addition of Me_2CuLi to **9** afforded the ketone **10** in nearly quantitative yield. The desired enone **11** was obtained in excellent yield by treatment of **10** with 10% HCl and subsequent intramolecular aldol condensation of the crude diketone.

We assumed that the remaining quaternary carbon at C-4 with the desired stereochemistry could be constructed by an attack of a vinyl cuprate such as $(vinyl)_2Cu(CN)Li_2$[9] from the less hindered side of **11** (Scheme 1). As shown in Scheme 2, we simply investigated the conjugate addition of a vinyl cuprate to some enones. Treatment of isophorone **13** with $(vinyl)_2Cu(CN)Li_2$ yielded a vinylated product **14** in 60% yield. The enone **15** (vide infra) bearing the same skeleton as **11** also gave **16** (68% yield); however, formation of the undesired 4,10-*cis* isomer predominated (*cis*/*trans*=5:1).[10] In the case of **11**, the vinylation proceeded hardly (<10% yield) under similar reaction conditions. Increased loading of vinyl cuprate or prolonged reaction



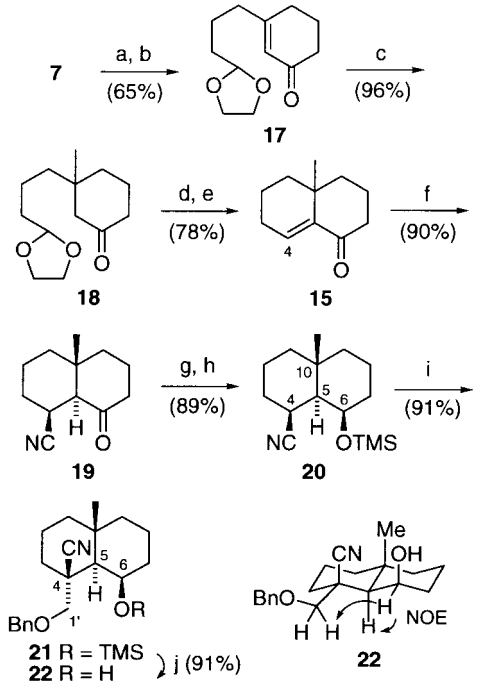
Scheme 1. *Reaction conditions*: (a) Li, 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, THF, ultrasound, rt; (b) PCC, Al_2O_3, CH_2Cl_2, rt; (c) Me_2CuLi, Et_2O, −20→0°C; (d) HCl, MeOH, 65°C; (e) TSA, PhH, Dean–Stark, 110°C.



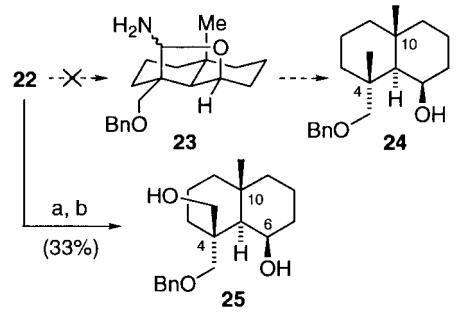
Scheme 2. *Reaction and condition*: $(vinyl)_2Cu(CN)Li_2$, −78°C→0°C.

time had no effect. Moreover, the small amount of the vinylated product formed was an inseparable mixture of two isomers. Other reagents such as $(vinyl)_2Cu(CN)Li_2{\cdot}2LiCl$, $(vinyl)_2Cu(CN)(ZnCl)_2{\cdot}4LiCl$,[11] or (vinyl)MgBr–CuBr·DMS[4b] were also ineffective. We reasoned that the presence of both methyl groups at C-4 and C-10 prevented the reagent from reacting with the substrate, presumably due to steric hindrance.

Due to very low yield and formation of an intractable mixture of the vinylated ketones, we next planned a different route. We synthesized a similar enone **15** lacking a methyl substituent at C-4 in the same way (Scheme 3). Barbier reaction of **7**, subsequent oxidation,



Scheme 3. *Reaction conditions*: (a) Li, 2-(-3-chloropropyl)-1,3-dioxolane, THF, ultrasound, rt (67%); (b) PCC, Al_2O_3, CH_2Cl_2, rt (97%); (c) Me_2CuLi, Et_2O, −20→0°C; (d) HCl, MeOH, 65°C; (e) TSA, PhH, Dean–Stark device, 110°C (78%, two steps); (f) Et_2AlCN, TMSCl, PhH, 0°C; (g) $NaBH_4$, MeOH–THF (2:1), rt (100%); (h) TMSCl, pyridine, DMAP, CH_2Cl_2, 0°C (89%); (i) LDA, BOMCl, THF, −78→0°C; (j) TBAF, THF, 45°C.



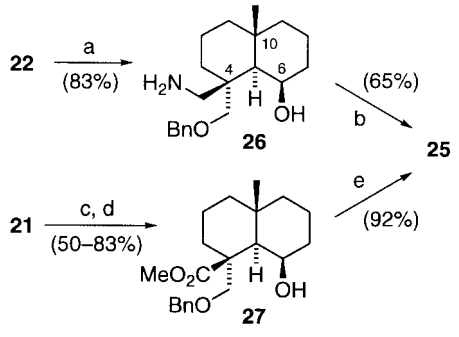
Scheme 4. *Reaction conditions*: (a) $LiAlH_4$, THF, −78°C→reflux; (b) $H_2N–NH_2·H_2O$, diethylene glycol, 195°C, then KOH, 210°C.

and 1,4-addition of methyl group to the enone **17** afforded the ketone **18**. Acid treatment of **18** furnished the enone **15** in good yield.

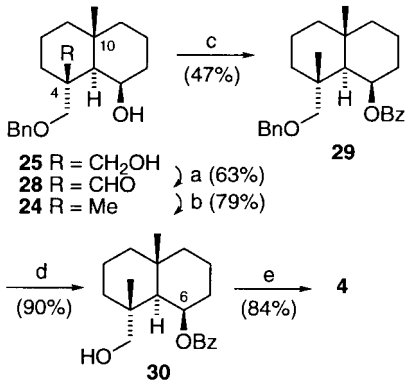
With this enone **15** in hand, we explored a different route via a conjugate addition of a cyano group and stereoselective α-alkylation.[12] Thus, treatment of the enone **15** with Et_2AlCN in benzene provided the desired nitrile **19** along with some of the A/B-*cis* product.[13] However, when the reaction was conducted in the presence of TMSCl in benzene, **19** was obtained as a single isomer. Reduction of the ketone **19** and TMS protection of the resulting alcohol proceeded to give the silyl ether **20** with the requisite stereochemistry, in excellent yields. The stereochemistry of **20** was confirmed by NOE analyses. Irradiation of the signals of the 4-H led to NOE enhancement of the signals of 5-H and 6-H. In contrast, no NOE was observed between 10-methyl and 4-H, 5-H, or 6-H. After several attempts to generate a quaternary carbon at C-4, a convenient strategy reported by Overman was followed (Scheme 3).[4c] Stereoselective alkylation was performed by treating the nitrile **20** with LDA and freshly distilled benzyloxymethyl chloride.[14] Deprotection of the TMS group afforded the alcohol **22**. The stereochemistry was confirmed in this stage by NOE analysis. Strong NOE enhancement of 5-H and 1′-H was observed when 6-H was irradiated (see the structure **22** in Scheme 3).

2.2. Conversion of the hindered cyano group into a methyl group and subsequent functional group modifications

Our next plan was the conversion of the axial hindered



Scheme 5. *Reaction conditions*: (a) $LiAlH_4$, THF, −78→75°C; (b) KOH, diethylene glycol, 210°C; (c) KOH, K_2CO_3, 140°C; (d) $TMSCHN_2$, Et_2O, 0°C; (e) $LiAlH_4$, THF, 0°C.



Scheme 6. *Reaction conditions*: (a) $RuCl_2(PPh_3)$ (0.8 equiv.), PhH, rt; (b) K_2CO_3, $H_2N–NH_2·H_2O$, diethylene glycol, 170→210°C; (c) BzOTf, 2,6-lutidine, CH_2Cl_2 0°C; (d) H_2, Pd/C, MeOH, rt; (e) Jones reagent, acetone, rt.

cyano group into a methyl group. We speculated that the partial reduction of the nitrile **22** by $LiAlH_4$ would produce the aminal **23**, which would give the desired 4,10-dimethylated alcohol **24** by Wolff–Kishner reduction (Scheme 4).[5b] However, the desired conversion did not proceed. Rather, we found that the diol **25** was unexpectedly formed in low yield upon exposure of the crude mixture obtained by $LiAlH_4$ reduction of **22** to the Wolff–Kishner conditions. Further experiments revealed that the product obtained by $LiAlH_4$-reduction was a primary amine instead of the aminal **23**, and that the amine was then converted into the primary alcohol **25** under the basic condition. Since Overman in his total synthesis of scopadulcic acid B described an efficient formation of an aminal using a similar nitrile whose cyano group is located at C-10 instead of C-4,[5b] we could not explain the cause of this unsuccessful result. Although we investigated other conversion methods of the cyano group into a methyl[15] or formyl group[16] (limonene–Pd/C,[15] $LiAlH_4$,[16a,b] $FeCl_3$–Isopropyl chloride,[16c] DIBAL-H, etc.), all our attempts were unsuccessful.

Next, we turned our attention to the formation of the alcohol **25** from the amine **26** (Scheme 5). After considerable experimentation, we found that the diol **25** could be obtained in 65% yield from the amine **26** by treating with KOH in diethylene glycol at 210°C.[8] At the same time, we also investigated other routes for efficient conversion of the nitrile **21** to the diol **25**. Thus, hydrolysis of the cyano group of **21** into a carboxyl group, esterification, and subsequent $LiAlH_4$ reduction of the resulting ester provided the diol **25** in good yields. It should be noted that we observed variable yields (50–83%) in the conversion of **21** into **27**.

After the synthesis of the diol **25**, we completed the synthesis of the model compound **4** via the 4,10-dimethyl derivative **24** (Scheme 6).[17] The primary hydroxy group of **25** was selectively oxidized by $RuCl_2(PPh_3)_3$[18] to yield the aldehyde **28** (63% yield) together with the recovered starting material (33%). The aldehyde was then reduced to a methyl group by Huang–Minlon reduction[19] to give **24** in 79% yield. The conventional benzoylation of the secondary alcohol of **24** using BzCl–pyridine was sluggish (20% yield; reflux, 28 h). Although benzoylation using freshly prepared BzOTf[20] and pyridine was also unsatisfactory (27%), an improved yield was obtained using BzOTf and 2,6-lutidine (47%). The

benzyl group of **29** was removed, and Jones oxidation of the resulting primary alcohol of **30** afforded the compound **4** with all the desired functionalities.

3. Conclusion

Toward the total synthesis of scopadulin, we have established an efficient route for stereoselective construction of the A/B ring system model with the desired functionalities. Stereoselective cyanation of a bicyclic enone followed by α-alkylation of the resulting nitrile afforded the nitrile bearing a quaternary carbon center at C-4 with the desired stereochemistry. Conversion of the cyano into a methyl group, and appropriate modification of functional groups yielded the model compound of scopadulin with all the desired functionalities. Application of this efficient route to the total synthesis of (±)-scopadulin is now being investigated in this laboratory.

4. Experimental

4.1. General methods

Melting points are uncorrected. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s=singlet, d=doublet, dd=double doublet, ddd=doublet of double doublet, t=triplet, dt=double triplet, m=multiplet). For column chromatography, silica gel 60 (0.063–0.200 mm, Merck) was employed. For flash chromatography, silica gel 60 (0.040–0.063 mm, Merck) was employed. THF, CH_2Cl_2, and benzene were freshly distilled prior to use.

4.1.1. 1-[3-(1-Methyl-2,5-dioxolanyl)propyl]cyclohex-2-en-1-ol (8). Li dispersion (30%; 188 mg, 2.44 mmol), washed with dry hexane, was suspended in THF (6 mL) under argon. **7** (97%, 0.20 mL, 2.00 mmol) and 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (0.50 mL, 3.20 mmol) were added. The mixture was sonicated for 30 min on an ultrasonic bath. The mixture was cooled to 0°C, Li was quenched by water, and the resulting mixture was neutralized by aqueous NH_4Cl. The whole was extracted with EtOAc, and the extract was washed with water and brine, dried ($MgSO_4$), and concentrated. The concentrate was purified by column chromatography (1:1 hexane/EtOAc) to give 324 mg (72%) of **8** as a colorless oil. IR (KBr) cm^{-1}: 3466, 1647, 1142. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.32 (s, 3H), 1.45–1.72 (m, 11H), 1.92–1.95 (m, 1H), 2.02–2.05 (m, 1H), 3.91–3.97 (m, 4H), 5.63 (d, J=10.5 Hz, 1H), 5.80 (ddd, J=10.5, 4.0, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.2, 19.0, 23.7, 25.2, 34.4, 39.6, 42.3, 64.6 (2C), 69.7, 110.1, 129.9, 132.6. MS (EI) m/z (%): 226 (M^+, 0.2), 87 (100). HRMS (EI) Calcd for $C_{13}H_{22}O_3$: 226.1569. Found: 226.1577.

4.1.2. 3-[3-(1-Methyl-2,5-dioxolanyl)propyl]cyclohex-2-en-1-one (9). To a stirred suspension of PCC (564 mg, 2.62 mmol) and Al_2O_3 (523 mg) in CH_2Cl_2 (6 mL) was added a solution of **8** (302 mg, 1.34 mmol) in CH_2Cl_2 (2.5 mL) at 0°C. The reaction mixture was stirred at rt for 1 h. The mixture was filtered through a plug of celite eluting with hexane/EtOAc (1:1). The filtrate was concentrated. Purification of the concentrate by column chromatography (1:1 hexane/EtOAc) gave **9** (213 mg, 71%) as a colorless oil. IR (KBr) cm^{-1}: 1668, 1624, 1119. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.31 (s, 3H), 1.60–1.66 (m, 4H), 1.96–2.02 (m, 2H), 2.31 (t, J=7.0 Hz, 2H), 2.29 (t, J=6.0 Hz, 2H), 2.36 (t, J =7.0 Hz, 2H), 3.90–3.98 (m, 4H), 5.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.3, 22.7, 23.8, 29.6, 37.3, 38.0, 38.6, 64.7 (2C), 109.7, 125.8, 166.1, 199.8. MS (EI) m/z (%): 224 (M^+, 5.9), 209 (7.3), 87 (100). HRMS (EI) Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1415.

4.1.3. 3-Methyl-3-[3-(1-methyl-2,5-dioxolanyl)propyl]-cyclohexan-1-one (10). To a stirred suspension of CuI (1.41 g, 7.40 mmol) in Et_2O (13 mL) was added dropwise MeLi (1.14 M in Et_2O; 12.9 mL, 14.8 mmol) at −20°C and the mixture was stirred for 15 min. A solution of **9** (832 mg, 3.71 mmol) in Et_2O (3 mL) was then added dropwise at −10°C and the reaction mixture was warmed to 0°C. After stirring for 1.5 h at 0°C, the reaction mixture was neutralized by aqueous NH_4Cl. The whole was extracted with EtOAc (5 times). Finally, the combined organic phases were washed with water and brine, dried ($MgSO_4$) and concentrated. Purification of the concentrate by column chromatography (3:1 hexane/EtOAc) afforded **10** (858 mg, 96%) as a colorless oil. IR (KBr) cm^{-1}: 1709, 1115. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.89 (s, 3H), 1.15–1.40 (m, 4H), 1.28 (s, 3H), 1.49–1.63 (m, 4H), 1.80–1.86 (m, 2H), 2.08 (d, J=13.5 Hz, 1H), 2.16 (d, J=13.5 Hz, 1H), 2.23–2.27 (m, 2H), 3.87–3.94 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.9, 22.1, 23.8, 24.9, 35.8, 38.6, 39.8, 41.0, 42.0, 53.8, 64.6 (2C), 109.9, 212.1. MS (FAB) m/z (%): 241 (MH^+, 51), 87 (100). HRMS (FAB) Calcd for $C_{14}H_{25}O_3$ (MH^+): 241.1804. Found: 241.1818.

4.1.4. 6,10-Dimethylbicyclo[4.4.0]dec-1(10)-en-2-one (11). 10% HCl (5.4 mL) was added to a solution of **10** (838 mg, 3.49 mmol) in MeOH (10 mL), and the resulting mixture was heated at 65°C for 2 h. The reaction was neutralized by saturated $NaHCO_3$, and MeOH was evaporated. The aqueous layer was then extracted with EtOAc, and the extract was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was filtered through a short column of silica gel and the filtrate was concentrated. The concentrate was dissolved in benzene (110 mL), *p*-toluenesulfonic acid monohydrate (100 mg, 0.526 mmol) was added, and the resulting mixture was refluxed (Dean–Stark device) at 110°C for 8 h. The reaction mixture was washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by column chromatography (1:1 hexane/EtOAc) yielded **11** (553 mg, 89% in two steps) as a yellow oil. IR (KBr) cm^{-1}: 1684, 1624. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (s, 3H), 1.24–1.50 (m, 2H), 1.58–1.71 (m, 4H), 1.75 (s, 3H), 1.84–1.91 (m, 1H), 1.92–2.02 (m, 1H), 2.02–2.07 (m, 2H), 2.31 (ddd, J=15.0, 13.0, 7.5 Hz, 1H), 2.49 (ddd, J=15.0, 5.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.3, 20.8, 25.3, 26.7, 31.8, 33.2, 38.3, 40.2, 43.3, 122.5, 130.0, 206.4. MS (EI) m/z (%): 178 (M^+, 100). HRMS (EI) Calcd for $C_{12}H_{18}O$: 178.1358. Found: 178.1377.

4.1.5. 3-[3-(2,5-Dioxolanyl)propyl]cyclohex-2-en-1-one (17). By a procedure similar to that described for the preparation of **8** from **7**, **7** (97%, 1.35 mL, 13.5 mmol) was converted into 1-[3-(2,5-dioxolanyl)propyl]cyclohex-2-en-1-ol (1.92 g, 67%) as a colorless oil. IR (KBr) cm^{-1}: 3462, 1706, 1142. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.45–1.71 (m, 11H), 1.88–1.92 (m, 1H), 1.99–2.10 (m, 1H), 3.79–3.86 (m, 2H), 3.91–3.98 (m, 2H), 4.84 (t, J=5.0 Hz, 1H), 5.60 (d, J=10.0 Hz, 1H), 5.77 (ddd, J=10.0, 5.0, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.2, 19.0, 25.2, 34.3, 35.4, 42.1, 64.8 (2C), 69.6, 104.5, 130.0, 132.6. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.90; H, 9.39. According to the procedure for the synthesis of **9** from **8**, 1-[3-(2,5-dioxolanyl)-propyl]cyclohex-2-en-1-ol (1.0 g, 4.71 mmol) was converted into **17** (963 mg, 97%) as a colorless oil. IR (KBr) cm^{-1}: 1668, 1624, 1140. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.58–1.68 (m, 4H), 1.93–1.98 (m, 2H), 2.22–2.27 (m, 4H), 2.32 (t, J=6.5 Hz, 2H), 3.79–3.85 (m, 2H), 3.89–3.96 (m, 2H), 4.84 (t, J=4.5 Hz, 1H), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.2, 22.7, 29.6, 33.2, 37.3, 37.7, 64.9 (2C), 104.1, 125.9, 165.8, 199.8. MS (EI) m/z (%): 210 (M^+, 4.1), 99 (29.7), 73 (100). HRMS (EI) Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1266.

4.1.6. 3-[3-(2,5-Dioxolanyl)propyl]-3-methylcyclohexan-1-one (18). By a procedure similar to that described for the preparation of **10** from **9**, **17** (460 mg, 2.19 mmol) was converted into **18** (475 mg, 96%) as a colorless oil. IR (KBr) cm^{-1}: 1709, 1142. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.89 (s, 3H), 1.21–1.29 (m, 2H), 1.30–1.40 (m, 2H), 1.48–1.53 (m, 1H), 1.57–1.64 (m, 3H), 1.78–1.87 (m, 2H), 2.07 (d, J=13.4 Hz, 1H), 2.16 (d, J=13.4 Hz, 1H), 2.19–2.28 (m, 2H), 3.78–3.85 (m, 2H), 3.89–3.96 (m, 2H), 4.81 (t, J=4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.9, 22.1, 24.9, 34.4, 35.7, 38.6, 41.0, 41.6, 53.7, 64.8 (2C), 104.4, 212.1. MS (FAB) m/z (%): 227 (MH^+, 100). HRMS (FAB) Calcd for $C_{13}H_{23}O_3$ (MH^+): 227.1647. Found: 227.1657.

4.1.7. 6-Methylbicyclo[4.4.0]dec-1(10)-en-2-one (15). Aqueous HCl (10%; 2.7 mL) was added to a solution of **18** (392 mg, 1.73 mmol) in MeOH (5 mL), and the resulting mixture was heated at 65°C for 4 h. The reaction was neutralized by saturated $NaHCO_3$, and MeOH was evaporated. The aqueous layer was then extracted with EtOAc, and the extract was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (3:7→3:2 EtOAc/hexane) to give 230 mg (73%) of 10-hydroxy-6-methylbicyclo-[4.4.0]decan-2-one along with 54 mg (19%) of **15** as an oil. 10-Hydroxy-6-methylbicyclo[4.4.0]decan-2-one: IR (KBr) cm^{-1}: 3412, 1705. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.94 (s, 3H), 1.12–1.24 (m, 3H), 1.51 (dt, J=14.0, 3.0 Hz, 1H), 1.60–1.68 (m, 2H), 1.78–2.10 (m, 6H), 2.25–2.29 (m, 1H), 2.54 (td, J=14.0, 7.0 Hz, 1H), 4.01 (td, J=11.0, 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.9, 22.0, 28.0, 30.2, 35.2, 37.3, 38.7, 39.2, 67.6, 69.8, 214.1. MS (EI) m/z (%): 182 (M^+, 1.5), 111 (100). HRMS (EI) Calcd for $C_{11}H_{18}O_2$: 182.1307. Found: 182.1326. To a solution of the above alcohol (250 mg, 1.37 mmol) in benzene (25 mL) was added p-TsOH·H_2O (38 mg, 0.2 mmol) under stirring. The resulting mixture was refluxed (Dean–Stark device) at 110°C for 1.5 h. The mixture was then washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by column chromatography (2:1 hexane/EtOAc) yielded **15** (181 mg, 81% combined yield; 78% in two steps) as an oil. IR (KBr) cm^{-1}: 1682, 1620. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.02 (s, 3H), 1.40 (td, J=12.5, 4.5 Hz, 1H), 1.51–1.61 (m, 2H), 1.64–1.70 (m, 3H), 1.83–1.88 (m, 1H), 1.93–2.02 (m, 1H), 2.08–2.20 (m, 2H), 2.26 (ddd, J=16.5, 12.5, 7.5 Hz, 1H), 2.50–2.55 (m, 1H), 6.36 (dd, J=4.5, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.8, 19.3, 25.5, 25.9, 35.6, 37.8, 38.9, 40.4, 133.2, 144.6, 202.9. MS (EI) m/z (%): 164 (M^+, 100). HRMS (EI) Calcd for $C_{11}H_{16}O$: 164.1201. Found: 164.1211.

4.1.8. (1*S,2*S**,6*R**)-6-Methyl-10-oxobicyclo[4.4.0]-decane-2-carbonitrile (19).** A solution of **15** (315 mg, 1.92 mmol) in benzene (5 mL) was added dropwise to a solution of Et_2AlCN (1.0 M in toluene, 5.7 mL) under stirring at 0°C. After being stirred at 0°C for 2 h, a viscous solution of Et_3N (2.60 mL, 18.7 mmol) and TMSCl (1.20 mL, 9.53 mmol) in benzene (1.5 mL) was added using a canula. The resulting mixture was warmed to rt, and Et_2O (80 mL) and saturated aqueous $NaHCO_3$ (35 mL) were added carefully. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (K_2CO_3), filtered and concentrated to give the crude silyl enol ether. The concentrate was then dissolved in 10:1 THF–H_2O (17 mL) and 1N HCl (0.17 mL) was added and the mixture was stirred at rt for 15 min. The resulting mixture was diluted with ether (40 mL), and K_2CO_3 (533 mg) was added. The mixture was stirred for 10 min, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (3:1 hexane/EtOAc) gave 330 mg (90%) of **19** as a colorless solid. Recrystallization (hexane/Et_2O) provided an analytically pure coarse powder: mp 95–96°C. IR (KBr) cm^{-1}: 2235, 1712. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.10 (s, 3H), 1.31 (td, J=14.0, 4.5 Hz, 1H), 1.50 (tt, J=14.0, 4.5 Hz, 1H), 1.56–1.64 (m, 4H), 1.80–1.90 (m, 1H), 1.92–2.01 (m, 2H), 2.10 (d, J=14.6 Hz, 1H), 2.23–2.30 (m, 2H), 2.45 (dt, J=14.6, 3.3 Hz, 1H), 2.97 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.1, 18.7, 21.4, 23.4, 29.4, 39.4, 39.8, 40.5, 41.9, 57.3, 121.6, 208.0. MS (EI) m/z (%): 191 (M^+, 32), 111 (100). HRMS (EI) Calcd for $C_{12}H_{17}NO$: 191.1310. Found: 191.1334.

4.1.9. (1*S,2*S**,6*R**,10*R**)-10-hydroxy-6-methyl-bicyclo[4.4.0]decane-2-carbonitrile.** To a solution of **19** (135 mg, 0.706 mmol) in MeOH–THF (2:1, 5 mL) was added $NaBH_4$ (35 mg, 0.925 mmol) at 0°C. The mixture was warmed to rt and stirred for 1 h. Aqueous NH_4Cl (excess) was added. The whole was concentrated, and the concentrate was extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The concentrate was purified through a short silica gel column (1:1 hexane/EtOAc) to provide 136 mg (100%) of the title compound as a colorless oil. IR (KBr) cm^{-1}: 3508, 2235. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.03–1.10 (m, 2H), 1.30–1.61 (m, 7H), 1.41 (s, 3H), 1.82 (d, J=3.5 Hz, 1H), 1.84–1.98 (m, 3H), 2.06–2.11 (m, 1H),

2.75 (m, 1H), 3.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.6, 18.8, 20.1, 29.0, 31.4, 34.6, 34.9, 43.0, 43.3, 48.6, 71.6, 123.6. MS (EI) *m/z* (%): 193 (M^+, 11.2), 95 (100). HRMS (EI) Calcd for $C_{12}H_{19}NO$ (M^+): 193.1467. Found: 193.1471.

4.1.10. (1*S,2*S**,6*R**,10*R**)-6-Methyl-10-(trimethylsiloxy)bicyclo-[4.4.0]decane-2-carbonitrile (20).** To a solution of (1*S**,2*S**,6*R**,10*R**)-10-hydroxy-6-methylbicyclo[4.4.0]decane-2-carbonitrile (53 mg, 0.274 mmol) in CH_2Cl_2 (1.5 mL) was added DMAP (8.35 mg, 0.068 mmol) and pyridine (0.46 mL) at 0°C. TMSCl (0.127 mL, 1.00 mmol) was then added and stirred at 0°C for 1.5 h. Saturated $NaHCO_3$ (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated. The concentrate was purified by column chromatography (3:1 hexane/Et_2O) to give **20** (64.5 mg, 89%) as a white solid. Recrystallization from hexane–Et_2O provided analytically pure **20** as colorless needles. Mp 74–75°C. IR (KBr) cm^{-1}: 2357. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.14 (s, 9H), 1.00–1.06 (m, 2H), 1.19 (dd, *J*=4.0, 2.5 Hz, 1H), 1.33–1.41 (m, 4H), 1.37 (s, 3H), 1.52–1.64 (m, 2H), 1.74–1.77 (m, 1H), 1.85–1.92 (m, 2H), 2.06–2.09 (m, 1H), 2.58–2.62 (m, 1H), 3.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.01 (3C), 16.7, 18.9, 20.1, 29.5, 32.0, 34.7, 34.9, 43.0, 43.7, 49.1, 71.4, 123.1. MS (FAB) *m/z* (%): 266 (MH^+, 100), 250 (55). HRMS (FAB) Calcd for $C_{15}H_{28}NOSi$ (MH^+): 266.1940. Found: 266.1942. Anal. Calcd for $C_{15}H_{27}NOSi$: C, 67.87; H, 10.25; N, 5.28. Found: C, 68.03; H, 10.11; N, 5.29.

4.1.11. (1*R,2*R**,6*R**,10*R**)-2-(Benzyloxymethyl)-6-methyl-10-(trimethylsiloxy)bicyclo[4.4.0]decane-2-carbonitrile (21).** To a stirred solution of diisopropylamine (0.105 mL, 0.749 mmol) in THF (0.85 mL), *n*-BuLi (1.6 M in hexane; 0.46 mL, 0.736 mmol) was added dropwise at −78°C, and the mixture was warmed to 0°C for 30 min. Then a solution of **20** (85 mg, 0.32 mmol) in THF (0.85 mL) was added dropwise and the resulting solution was stirred for 20 min. The yellow solution obtained was cooled to −78°C and freshly distilled benzyloxymethyl chloride (0.085 mL, 0.61 mmol) was added rapidly. The reaction mixture was warmed to 0°C. After stirring at 0°C for 1.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (excess). The whole was then extracted with EtOAc, and the extract was washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by flash chromatography (60:1 hexane/EtOAc) yielded 112 mg (91%) of **21** as a colorless oil. IR (KBr) cm^{-1}: 2231. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.07 (s, 9H), 1.07 (t, *J*=12.8 Hz, 2H), 1.40 (s, 3H), 1.32–1.42 (m, 4H), 1.58 (m, 1H), 1.72–2.02 (m, 6H) 3.42 (d, *J*=9.0 Hz, 1H), 3.57 (d, *J*=9.0 Hz, 1H), 4.00 (m, 1H), 4.46 (d, *J*=12.3 Hz, 1H), 4.60 (d, *J*=12.3 Hz, 1H), 7.30–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.34, 16.5, 19.1, 20.5, 34.6, 34.7, 36.1, 38.2, 43.1, 44.2, 49.2, 66.4, 72.7, 73.5, 123.3, 127.9 (2C), 128.0, 128.5 (2C), 137.5. MS (FAB) *m/z* (%): 386 (MH^+, 37), 91 (100). HRMS (FAB) Calcd for $C_{23}H_{35}NO_2Si$ (MH^+): 386.2515. Found: 386.2502.

4.1.12. (1*R,2*R**,6*R**,10*R**)-2-(Benzyloxymethyl)-10-hydroxy-6-methylbicyclo[4.4.0]decane-2-carbonitrile (22).** A solution of *n*-Bu_4NF (1.0 M in THF; 0.14 mL, 0.14 mmol) was added to a solution of **21** (25 mg, 0.065 mmol) in THF (0.6 mL) and the solution was heated at 45°C for 8 h. The reaction mixture was cooled to rt, Et_2O (2 mL) and brine (1.5 mL) was added and the mixture was stirred for 15 min. The organic phase was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified on silica gel column (5:1 hexane/EtOAc) to afford 18.5 mg (91%) of **22** as a colorless solid. Recrystallization from hexane provided pure **22**. Mp 90–91°C. IR (KBr) cm^{-1}: 3506, 2231. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.03–1.12 (m, 2H), 1.29 (d, *J*=2.5 Hz, 1H), 1.31–1.42 (m, 5H), 1.44 (s, 3H), 1.52–1.63 (m, 2H), 1.84–1.90 (m, 2H), 1.93–2.02 (m, 2H), 3.47 (d, *J*=8.8 Hz, 1H), 3.59 (d, *J*=8.8 Hz, 1H), 4.17 (m, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.57 (d, *J*=11.5 Hz, 1H), 7.27–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.5, 19.1, 20.4, 34.5, 34.6, 35.8, 38.7, 42.8, 44.1, 51.4, 66.5, 73.8, 74.4, 123.7, 127.8 (2C), 128.0, 128.5 (2C), 137.2. MS (EI) *m/z* (%): 313 (M^+, 5.4), 265 (9.3), 91 (100). HRMS (EI) Calcd for $C_{20}H_{27}NO_2$: 313.2042. Found: 313.2043.

4.1.13. (1*R,2*R**,6*R**,10*R**)-10-(Aminomethyl)-10-(benzyloxymethyl)-6-methylbicyclo[4.4.0]decan-2-ol (26).** To a solution of **22** (20 mg, 0.064 mmol) in THF (2.3 mL) was added $LiAlH_4$ (1.0 M in ether; 1.2 mL, 1.2 mmol) at −78°C, and the resulting mixture was warmed to rt and then refluxed for 4 h. The solution was cooled to 0°C, quenched by successive addition of H_2O (47 μl), 2N NaOH (47 μL) and H_2O (146 μL). The resulting heterogeneous mixture was stirred at rt for 2 h, filtered, and the solid was washed with EtOAc. The combined filtrates were concentrated. Crystallization from hexane yielded **26** (16.8 mg, 83%) as white granules. Mp 92–94°C. IR (KBr) cm^{-1}: 3369, 3292, 1587. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.06–1.59 (m, 11H), 1.35 (s, 3H), 1.70–1.74 (m, 1H), 1.89–1.98 (m, 2H), 2.79 (d, *J*=12.8 Hz, 1H), 3.14 (d, *J*=9.0 Hz, 1H), 3.22 (d, *J*=12.8 Hz, 1H), 3.57 (d, *J*=9.0 Hz, 1H), 4.05 (m, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 7.28–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.1, 18.2, 22.6, 34.6, 34.9, 38.0, 42.5, 43.4, 44.5, 47.0, 52.9, 64.6, 73.3, 76.7, 127.4 (2C), 127.6, 128.4 (2C), 138.6. MS (EI) *m/z* (%): 317 (M^+, 6.8), 91 (100). HRMS (EI) Calcd for $C_{20}H_{31}NO_2$: 317.2355. Found: 317.2353.

4.1.14. (1*R,2*R**,6*R**,10*R**)-10-(Benzyloxymethyl)-10-(hydroxymethyl)-6-methylbicyclo[4.4.0]decan-2-ol (25).** A mixture of **26** (10 mg, 0.0315 mmol), KOH (100 mg, 1.75 mmol, excess) and diethylene glycol (0.6 mL) were placed in a round-bottom flask equipped with a refluxing condenser and the mixture was heated at 210°C for 3 h. The black solution was then cooled to rt, Et_2O (2 mL) and H_2O (1.5 mL) were added. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were then washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chromatography (5:1 hexane/EtOAc) gave 6.5 mg (65%) of **25**. Recrystallization from hexane/Et_2O provided an analytically pure white solid: mp 139°C. IR (KBr) cm^{-1}: 3236 (br). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.33 (s, 3H), 1.06–1.59 (m, 11H), 1.84–1.87 (m, 1H), 1.90–1.99 (m,

1H), 3.39 (d, J=9.0 Hz, 1H), 3.47 (d, J=12.5 Hz, 1H), 3.48 (d, J=9.0 Hz, 1H), 4.14 (br s, 2H), 4.20 (s, 1H), 4.21 (d, J=12.5 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 1H), 7.27–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.9, 18.4, 22.3, 34.6, 35.4, 35.6, 42.7, 44.5, 46.2, 52.2, 66.2, 66.3, 73.5, 78.2, 127.5 (2C), 127.6, 128.4 (2C), 138.3. MS (FAB) m/z (%): 319 (MH^+, 25), 91 (100). HRMS (FAB) Calcd for $C_{20}H_{31}O_3$ (MH^+): 319.2273. Found: 319.2269.

4.1.15. Methyl (1*R,2*S**,6*R**,10*R**)-2-(benzyloxymethyl)-10-hydroxy-6-methylbicyclo[4.4.0]decane-2-carboxylate (27).** To a solution of **21** (27 mg, 0.070 mmol) in MeOH (2.3 mL) were added KOH (176 mg, excess) and K_2CO_3 (75 mg), and the mixture was concentrated by a stream of N_2. The residue was then heated at 140°C for 24 h. After cooling, the resulting residue was dissolved in water (6 mL), and Et_2O (6 mL) was added. The mixture was cooled to 0°C and acidified to pH 2 by 1N HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL×5). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give the crude acid. The crude acid was then dissolved in dry Et_2O (4 mL), and $TMSCHN_2$ (2.0 M in hexane, 90 μL, 0.18 mmol) was added at 0°C. After 30 min the mixture was concentrated. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give **27** (20.2 mg, 83%) as a colorless oil. IR (KBr) cm^{-1}: 3448, 1730. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.02 (s, 3H), 1.09–1.52 (m, 8H), 1.63 (s, 1H), 1.78–1.88 (m, 1H), 1.90–1.99 (m, 2H), 2.44–2.48 (m, 1H), 3.41 (d, J=8.5 Hz, 1H), 3.75 (d, J=8.5 Hz, 1H), 3.77 (s, 3H), 4.25 (m, 1H), 4.44 (d, J=12.5 Hz, 1H), 4.51 (d, J=12.5 Hz, 1H), 5.43 (d, J=2.5 Hz, 1H), 7.27–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.4, 19.4, 20.9, 34.3, 34.7, 35.2, 44.4, 44.8, 50.7, 52.6, 52.8, 65.2, 73.8, 77.7, 127.3, 127.6 (2C), 128.3, 138.0 (2C), 179.5. MS (EI) m/z (%): 346 (M^+, 0.1), 91 (100). HRMS (EI) Calcd for $C_{21}H_{30}O_4$: 346.2144. Found: 346.2126.

4.1.16. Preparation of the diol (25) from (27). To a solution of **27** (38 mg, 0.1098 mmol) in THF (1.6 mL) was added a solution of $LiAlH_4$ (1.0 M in Et_2O; 0.4 mL, 0.4 mmol) at 0°C. The resulting mixture was stirred at 0°C for 2 h. The mixture was quenched by a sequential addition of H_2O (20 μL), 2N NaOH (20 μL), and H_2O (83 μL) and the resulting heterogeneous mixture was then stirred at rt for 1 h. The mixture was filtered and the solid was washed with EtOAc. The combined organic layers were concentrated and the concentrate was purified by column chromatography (1:1 hexane/EtOAc) to provide **25** (32 mg, 92%) as a white solid.

4.1.17. (1*R,2*S**,6*R**,10*R**)-2-(Benzyloxymethyl)-10-hydroxy-6-methylbicyclo[4.4.0]decane-2-carbaldehyde (28).** $RuCl_2$-$(PPh_3)_3$ (30 mg, 0.031 mmol) was added to a solution of **25** (12 mg, 0.0377 mmol) in benzene (0.9 mL), and the resulting mixture was stirred at rt for 24 h. The black solution obtained was concentrated and the residue was chromatographed on silica gel (3:1 hexane/EtOAc) to afford **28** (7.5 mg, 63%) as a thick oil, together with 3.9 mg (33%) of recovered **25**. Compound **28**: IR (KBr) cm^{-1}: 3477, 1708. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.03 (s, 3H), 1.10–1.15 (m, 2H), 1.32–1.48 (m, 6H), 1.59–1.70 (m, 2H), 1.87–1.94 (m, 2H), 2.38 (d, J=14.5 Hz, 1H), 3.32 (s, 1H), 3.43 (d, J=8.5 Hz, 1H), 3.59 (d, J=8.5 Hz, 1H), 4.26 (m, 1H), 4.42 (d, J=12.0 Hz, 1H), 4.48 (d, J=12.0 Hz, 1H), 7.26–7.36 (m, 5H), 10.10 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.5, 18.7, 22.4, 32.9, 34.5, 35.1, 43.5, 44.1, 52.7, 53.7, 66.4, 73.7, 75.6, 127.5 (2C), 127.8, 128.4 (2C), 137.7, 211.4. MS (FAB) m/z (%): 339 (MNa^+, 48), 91 (100). HRMS (FAB) Calcd for $C_{20}H_{28}NaO_3$ (MNa^+): 339.1936. Found: 339.1958.

4.1.18. (1*R,2*R**,6*R**,10*R**)-10-(Benzyloxymethyl)-6,10-dimethylbicyclo[4.4.0]decan-2-ol (24).** A mixture of **28** (6 mg, 0.0189 mmol), K_2CO_3 (10 mg, 0.072 mmol), hydrazine monohydrate (0.2 mL) in diethylene glycol (0.8 mL) was refluxed at 170°C. After 2 h at 170°C, the reaction flask was opened and heated to 190°C to distill out excess hydrazine and water and again the reaction mixture was refluxed at 210°C for 2.5 h. The reaction mixture was cooled to rt, H_2O (1 mL) and Et_2O (1.5 mL) were added, and the mixture was neutralized by 1N HCl at 0°C. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the concentrate by column chromatography (5:1 hexane/EtOAc) provided 4.5 mg (79%) of **24** as a colorless oil. IR (KBr) cm^{-1}: 3548, 1602. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.06–1.87 (m, 14H), 1.14 (s, 3H), 1.27 (s, 3H), 3.00 (d, J=9.0 Hz, 1H), 3.36 (d, J=9.0 Hz, 1H), 4.20 (br, s, 1H), 4.45 (d, J=12.5 Hz, 1H), 4.51 (d, J=12.5 Hz, 1H), 7.28–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.9, 18.4, 20.0, 22.5, 34.4, 36.2, 38.1, 38.7, 44.2, 45.8, 49.9, 68.0, 73.2, 79.8, 127.4 (2C), 128.2, 128.3 (2C), 138.8. MS (FAB) m/z (%): 325 (MNa^+, 19), 91 (100). HRMS (FAB) Calcd for $C_{20}H_{30}NaO_2$ (MNa^+): 325.2143. Found: 325.2140.

4.1.19. (1*R,2*R**,6*R**,10*R**)-10-(Hydroxymethyl)-6,10-dimethylbicyclo[4.4.0]decan-2-yl benzoate (30).** To a solution of **24** (8 mg, 0.026 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise 2,6-lutidine (65 μL, 0.56 mmol) at 0°C. BzOTf (44 μL, 0.27 mmol) was then added dropwise and the resulting mixture was maintained at 0°C for 2 h. Et_2O (3 mL) and $NaHCO_3$ (0.3 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the concentrate by column chromatography (4:1 hexane/Et_2O) gave 5.0 mg (47%) of **29** as a colorless oil. Compound **29**: IR (KBr) cm^{-1}: 1724, 1603. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (s, 3H), 1.19–1.56 (m, 8H), 1.45 (s, 3H), 1.73–1.83 (m, 4H), 1.99 (d, J=14.0 Hz, 1H), 2.93 (d, J=9.0 Hz, 1H), 3.41 (d, J=9.0 Hz, 1H), 4.46 (d, J=12.3 Hz, 1H), 4.57 (d, J=12.3 Hz, 1H), 5.58 (m, 1H), 7.28–7.37 (m, 5H), 7.46 (t, J=7.5 Hz, 2H), 7.56 (t, J=7.5 Hz, 1H), 8.06–8.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.5, 18.4, 19.5, 22.6, 32.6, 34.6, 37.8, 38.5, 44.0, 45.2, 48.1, 71.0, 73.2, 78.8, 127.3 (2C), 127.4, 128.3 (2C), 128.4 (2C), 129.6 (2C), 131.1, 132.7, 138.9, 166.3. The compound **29** (8 mg, 0.0197 mmol) was subjected to catalytic hydrogenolysis over Pd/C (8 mg) in MeOH at atmospheric pressure overnight at rt. The reaction mixture was filtered, and the filtrate was concentrated. The concentrate was purified by column chromatography (2:1 hexane/

EtOAc) to give **30** (5.6 mg, 90%) as a colorless oil. IR (KBr) cm^{-1}: 3456, 1713, 1601. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (s, 3H), 1.15–1.62 (m, 10H), 1.46 (s, 3H), 1.65 (d, J=2.4 Hz, 1H), 1.74–1.87 (m, 2H), 2.00 (d, J=14.5 Hz, 1H), 3.16 (dd, J=10.5, 4.0 Hz, 1H), 3.60 (dd, J=10.5, 4.0 Hz, 1H), 5.64 (m, 1H), 7.44–7.48 (m, 2H), 7.55–7.59 (m, 1H), 8.06–8.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.5, 18.3, 19.1, 22.5, 32.7, 34.6, 37.9, 38.1, 44.1, 45.2, 48.1, 70.7, 71.3, 128.5 (2C), 129.6 (2C), 131.0, 132.8, 166.3. MS (FAB) *m/z* (%): 317 (MH^+, 20), 136 (100). HRMS (FAB) Calcd for $C_{20}H_{29}O_3$ (MH^+): 317.2117. Found: 317.2105.

4.1.20. (1*R,2*R**,6*R**,10*R**)-10-Benzoyloxy-6,10-dimethylbicyclo-[4.4.0]decane-2-carboxylic acid (4).** A solution of **30** (4 mg, 0.0126 mmol) in acetone (0.5 mL) was treated with Jones reagent dropwise until TLC indicated that no starting material was present. The reaction mixture was diluted with CH_2Cl_2, and the whole was washed with water and brine sequentially, dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by column chromatography (3:1 hexane/EtOAc) gave 3.5 mg (84%) of **4** as a white solid. Recrystallization (hexane) afforded a pure colorless solid: mp 182–183°C. IR (KBr) cm^{-1}: 2931 (br), 1716. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.28 (m, 4H), 1.34 (s, 3H), 1.48 (s, 3H), 1.56–1.88 (m, 8H), 2.05 (m, 1H), 2.09 (d, J=2.0 Hz, 1H), 5.37 (m, 1H), 7.46 (m, 2H), 7.56 (m, 1H), 8.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.5, 18.1, 22.3, 29.7, 32.3, 34.5, 39.8, 43.6, 45.3, 47.1, 49.6, 73.1, 128.2 (2C), 128.5 (2C), 130.9, 132.8, 166.1, 182.0. MS (FAB) *m/z* (%): 353 (MNa^+, 100). HRMS (FAB) Calcd for $C_{20}H_{26}NaO_4$ (MNa^+): 353.1729. Found: 353.1727.

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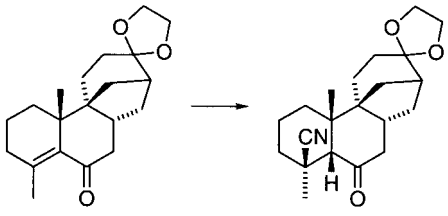
12. Construction of the quaternary carbon center with the desired stereochemistry has proven to be extremely difficult. Treatment of the β-methylated enone **31** with Et_2AlCN in benzene gave **32** with undesired stereochemistry. Therefore, we planned to introduce a cyano and benzyloxymethyl group at C-4 by a slight modification of the reported procedure by Overman: see Ref. 4c.



31 **32**

13. The undesired A/B-*cis* product was successively isomerized into **19** by treating with NaOMe.
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