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# Highly Efficient Stereocontrolled Synthesis of Danishefsky's Taxol CD Ring Key Intermediate

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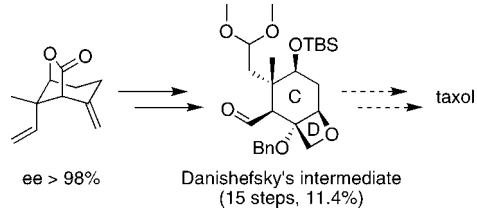


Danishefsky's taxol CD ring key intermediate is synthesized in 15 steps and 11.4% overall yield from a readily available starting material. Absolute stereochemistry of the starting material and stereocontrolled steps determine the absolute configuration of the five requisite contiguous stereocenters.

The tetracyclic diterpenoid paclitaxel (Taxol, Figure 1),[1] originally isolated from the Pacific yew tree *Taxus brevifolia*,[2] is a powerful therapeutic drug for cancer chemotherapy.[3] Particularly, this molecule and its synthetic analogue docetaxel (Taxotere, Figure 1)[4] exhibit strong antitumor activity against ovarian and breast cancers,[5,6] and additional exciting clinical uses are anticipated.[3c,7] Over the past two decades, important biological activity, limited supplies, and unique structural framework of taxol have attracted the attention of biologists, medicinal chemists, and synthetic chemists.

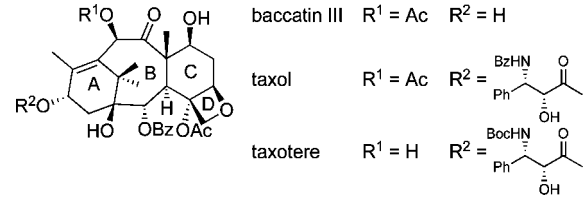


**FIGURE 1.** Structures of baccatin III, taxol, and taxotere.

The synthesis of taxol has presented one of the more difficult challenges to synthetic chemists, both because of its complex ring structure and because of its numerous chiral centers. As a consequence, tremendous efforts toward its synthesis have been made, which have so far resulted in six successful total syntheses of this molecule.[8–14] Among them, the elegant Danishefsky group synthesis[9] is the only one to start with a preformed CD ring system (+)-**1** (Scheme 1). This pivotal intermediate was coupled with an A ring synthon to afford the A-CD unit, and cyclization to the ABCD system was achieved by the Heck reaction. Subsequent appropriate oxidative chemistry and functional group manipulations led to baccatin III and taxol. The key to the success of this strategy was the discerning choice of protecting groups able to resist further chemical steps on the CD ring unit. Particularly, the protection of the C4 tertiary hydroxyl center as a benzyl ether rather than as an acetate, thus avoiding complications from neighboring group participation by this group later, was crucial (Scheme 2).

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(4) Taxotere is the registered trademark of Sanofi Aventis (Rhône-Poulenc Rorer Company) for docetaxel. (a) Mangatal, L.; Adeline, M. T.; Guénard, D.; Gueritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177–4190. (b) Gueritte-Voegelein, F.; Guénard, D.; Mangatal, L.; Potier, P.; Guilhem, J.; Cesario, M.; Pascard, C. *Acta Crystallogr.* **1990**, *C46*, 781–784. Review: (c) Guénard, D.; Gueritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160–167.

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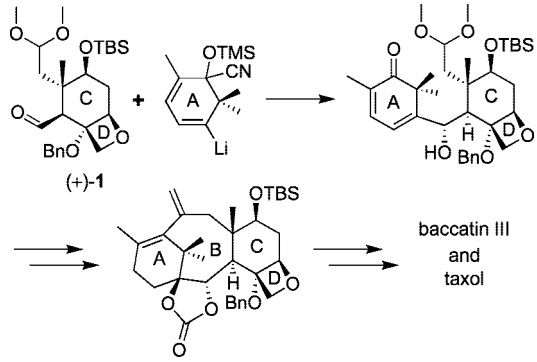
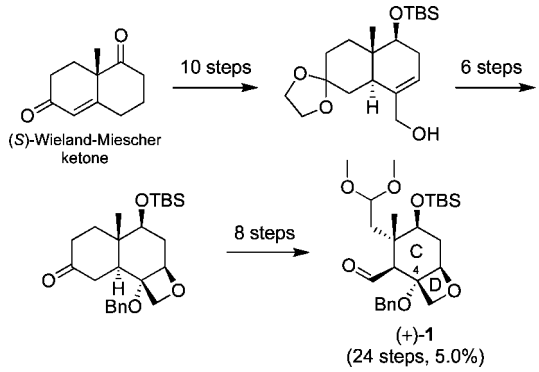
**SCHEME 1. Danishefsky's Convergent Synthesis of Baccatin III and Taxol**



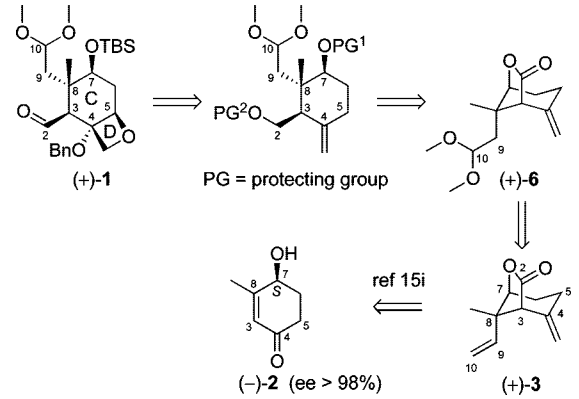

**SCHEME 2. Danishefsky's Synthesis of CD Ring Key Intermediate (+)-1**



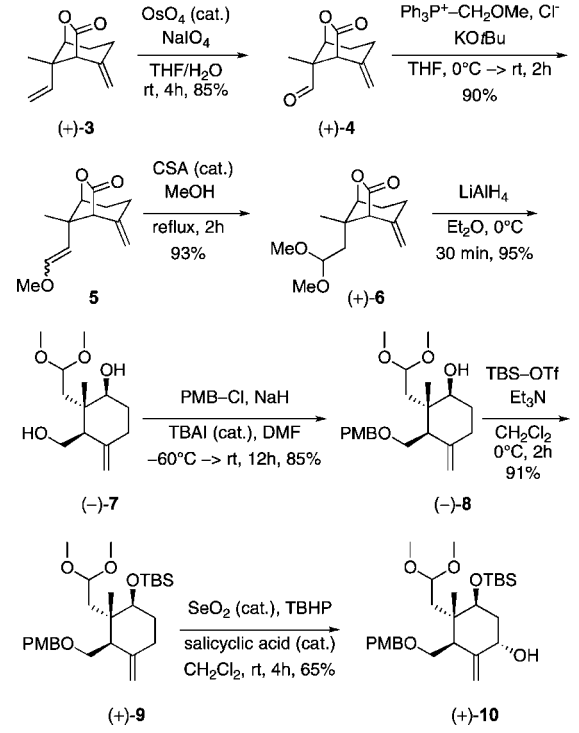

Although numerous approaches have been reported for the synthesis of the fully functionalized CD ring unit,[15] none of them presented functionalities suitable for elaboration into taxol following the Danishefsky strategy or have been used so far as part of a novel total synthesis of taxol.

Herein we describe an efficient and stereocontrolled[16] synthesis of the Danishefsky CD ring unit (+)-**1** based on the retrosynthetic analysis outlined in Scheme 3. The synthesis of (+)-**3**, readily available in multigram quantities, has been published first from enantiopure (−)-**2** obtained by kinetic enzymatic resolution.[15i] Subsequent to our initial success, we recently described a convenient chemoenzymatic enantioconvergent strategy which led to the formation of enantiopure (−)-**2**

**SCHEME 3. Retrosynthetic Analysis (Taxane Numbering)**




**SCHEME 4. Synthesis of Fully Protected Allylic Alcohol (+)-10**




with 100% theoretical yield from the racemate,[17] thus improving presently the former synthesis of (+)-**3**. Our plan was to first install the C9−C10 *gem*-dimethoxyethyl group to obtain (+)-**6** regioselectively. If successful, it was envisaged that this group would survive further reactions avoiding acidic conditions.

For this purpose, our synthetic efforts commenced with the attempts to hydroborate selectively the monosubstituted vinylic double bond in (+)-**3** in order to obtain (+)-**6** after oxidation of the primary alcohol and protection of the aldehyde. Unfortunately, no reaction occurred using substituted boranes such as 9-BBN or disiamylborane, and reaction with borane itself was almost completely nonselective, leading to a complex mixture. Due to the problems encoutered, we redesigned our strategy, and Scheme 4 outlines the chemistry involved. Thus, chemoselective oxidative cleavage of the vinyl double bond in (+)-**3** using $OsO_4$ (cat.) and $NaIO_4$ in THF/water (3:1) gave aldehyde (+)-**4** in 85% yield. Exposure of (+)-**4** to the

(15) Syntheses of the fully functionalized taxol CD ring unit: (a) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274–3276. (b) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1118–1120. (c) Isaacs, R. C. A.; Di Grandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938–3941. (d) Takahashi, T.; Hirose, Y.; Iwamoto, H.; Doi, T. *J. Org. Chem.* **1998**, *63*, 5742–5743. (e) Momose, T.; Setoguchi, M.; Fujita, T.; Tamura, H.; Chida, N. *Chem. Commun.* **2000**, 2237–2238. (f) Nakai, K.; Miyamoto, S.; Sasuga, D.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 7859–7862. (g) Yoshimitsu, T.; Nakajima, H.; Nagaoka, H. *Tetrahedron Lett.* **2002**, *43*, 8587–8590. (h) Shing, T. K. M.; Lee, C. M.; Lo, H. Y. *Tetrahedron* **2004**, *60*, 9179–9197. (i) Uttaro, J.-P.; Audran, G.; Monti, H. *J. Org. Chem.* **2005**, *70*, 3484–3489. Construction of the oxetane D ring in semisyntheses of taxanes: (j) Original Potier's procedure applied in numerous diversified methodologies: Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823–9838. (k) Zeng, Q.; Paquette, L. A. *Synlett* **1999**, 1547–1550. (l) Paquette, L. A.; Lo, H. Y. *J. Org. Chem.* **2003**, *68*, 2282–2289. (m) Brennan, N. K.; Guo, X.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 732–734.

(16) The Danishefsky strategy faced two unfortunate steps: (i) a surprising non-stereoselective osmylation leading to approximatively 15% of a wrong stereoisomer occurred, and (ii) a by-product arising from a pinacol-like rearrangement was formed in approximatively 14% yield during the cyclization of the desired oxetane.

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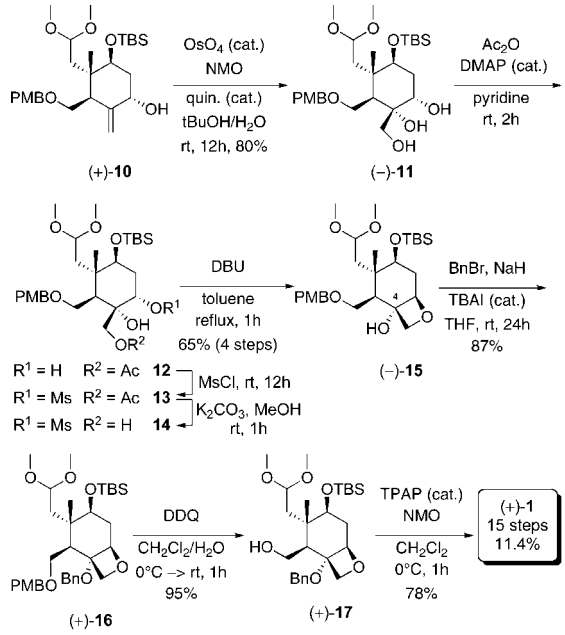
**SCHEME 5. Synthesis of CD Ring Key Intermediate (+)-1**




α-methoxy-substituted ylid, obtained by reacting methoxymethyltriphenylphosphonium chloride[18] with KO*t*Bu in THF afforded **5** as a mixture of stereomers in 90% yield, then refluxing the enol ethers with anhydrous methanol containing CSA produced the dimethyl acetal (+)-**6** in 93% yield. Reduction of the lactone functionality of (+)-**6** with $LiAlH_4$ in ether at 0 °C provided diol (−)-**7** in 95% yield.

At this stage, we had to protect the two hydroxy centers of compound (−)-**7**. Logically, protection of the secondary alcohol as a TBS ether present in the target molecule (+)-**1** should not be a problem, but we were mindful that the presence of the dimethyl acetal group restricted the scope of possible temporary protecting groups for the primary alcohol. Much would be expected from this protecting group, not the least demanding property being its susceptibility to removal at a late step of our strategy under essentially neutral conditions. On the basis of these considerations, we decided to install a PMB protecting group on the primary alcohol because PMB ethers are especially susceptible to oxidative cleavage under neutral reaction conditions (DDQ, $CH_2Cl_2$/water) to give the desired alcohol, whereas acetals and TBS ethers are generally stable to these conditions, though exceptions do occur. This installation was accomplished chemoselectively (PMBCl, NaH, cat. TBAI), giving rise to monoprotected (−)-**8** in 85% yield. The hindered secondary hydroxy group of the molecule was then protected as the TBS ether (TBS-OTf, $Et_3N$, 0 °C) to give the fully protected derivative (+)-**9**. Stereoselective allylic oxidation[19] of (+)-**9** from the less hindered α-face (cat. $SeO_2$, *t*BuOOH) afforded allylic alcohol (+)-**10** as a single isomer in 65% yield. The ensuing dihydroxylation of the methylene bond within (+)-**10** (NMO, cat. $OsO_4$, cat. quinuclidine) proceeded selectively from the face opposite the axial C8 methyl group, thus furnishing the expected triol (−)-**11** in 80% yield (Scheme 5).[15f] According to the reported procedure,[14] triol (−)-**11** was converted to oxetane (−)-**15** in four steps and 65% overall yield without isolation of intermediates as follows: temporary protection of the C20 hydroxy group as an acetate **12** ($Ac_2O$, cat. DMAP, Pyr.), formation of secondary C5α mesylate **13** (MsCl), hydrolysis of the temporary acetyl protecting group to give **14** ($K_2CO_3$, MeOH), and cyclization (DBU, refluxing toluene).

With oxetane (−)-**15** in hand, we had to install the C4 protecting group as the tertiary benzyl ether of the Danishefsky's taxol CD ring intermediate. For this purpose, (−)-**15** was treated with BnBr, NaH, and TBAI (cat.) to give (+)-**16** in 87% yield. At this junction, and to our delight, selective removal of the PMB group could be accomplished as wished with perfect chemoselective control and without any deprotection of the frail dimethyl acetal group. Thus, exposure of (+)-**16** to DDQ in $CH_2Cl_2$/water (9:1) afforded the corresponding primary alcohol (+)-**17** in 95% yield. Derivative (+)-**17** was finally converted into the requisite target molecule (+)-**1** in 78% yield and without any epimerization by treatment with TPAP (cat.) and NMO in $CH_2Cl_2$ at 0 °C.[20] Spectroscopic data and optical rotation of (+)-**1** perfectly matched those reported by Danishefsky and coworkers.

In conclusion, we have achieved a novel, highly efficient and fully stereocontrolled strategy to the Danishefsky taxol CD ring key intermediate in 15 steps and 11.4% overall yield from easily available (+)-**3**.[21] This approach further improves and shortens the original strategy of Danishefsky, thus highlighting his elegant and convergent total synthesis of taxol.

## Experimental Section

**(1*S*,3*R*,4*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-(2,2-dimethoxyethyl)-3-((4-methoxybenzyloxy)methyl)-4-methyl-2-methylenecyclohexanol (+)-10.** To an ice-cold stirred solution of (+)-**9** (500 mg, 1.04 mmol) in dry $CH_2Cl_2$ (20 mL) was added *tert*-butylhydroperoxide (434 μL, 3.13 mmol, 3.0 equiv, 70% in water) followed by a catalytic amount of selenium dioxide and salicylic acid under argon atmosphere. The mixture was stirred at rt for 4 h, then poured into an aqueous $Na_2SO_3$ solution. After extraction with ether, the organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by column chromatography gave (+)-**10** (336 mg, 65%) as a clear oil: $[\alpha]^{25}_D$ +8.6 (*c* 1.0, $CHCl_3$); IR (film) $\nu$ 3408, 3013, 1147, 1043 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.22 (br d, $J$ = 8.7 Hz, 2H), 6.85 (br d, $J$ = 8.7 Hz, 2H), 5.14 (br s, 1H), 4.90 (br s, 1H), 4.48 and 4.36 (AB, $J$ = 11.8 Hz, 2H), 4.46 (dd, $J$ = 10.3, 4.3 Hz, 1H, partially overlapped), 4.42−4.35 (m, 1H), 3.79 (s, 3H), 3.73−3.64 (m, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.60 (dd, $J$ = 8.5, 4.9 Hz, 1H), 1.85−1.71 (m, 3H), 1.52 (dd, $J$ = 14.6, 6.0 Hz, 1H), 0.88 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.9, 148.8, 130.6, 129.0 (2C), 113.5 (2C), 109.6, 102.4, 73.4, 72.3, 68.5, 67.5, 55.0, 52.7, 52.1, 49.6, 40.6, 40.0, 39.1, 25.7 (3C), 18.4, 17.8, 4.4, 5.2. Anal. Calcd for $C_{27}H_{46}O_6Si$: C, 65.55; H, 9.37. Found: C, 65.80; H, 9.41.

**(1*S*,2*S*,4*S*,5*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(2,2-dimethoxyethyl)-1-(hydroxymethyl)-6-((4-methoxybenzyloxy)methyl)-5-methylcyclohexane-1,2-diol (−)-11.** To an ice-cold solution of (+)-**10** (300 mg, 0.61 mmol) in 20 mL of *t*BuOH/$H_2O$ (3/1) was added *N*-methylmorpholine *N*-oxide (142 mg, 1.21 mmol, 2.0 equiv) followed by a catalytic amount of $OsO_4$ (4% in water) and a catalytic amount of quinuclidine. The resulting brown mixture was stirred at rt for 12 h, then poured into aqueous $Na_2SO_3$ solution. After extraction with ethyl acetate, the organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under

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(20) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

reduced pressure. Purification of the residue by column chromatography gave (−)-**11** (255 mg, 80%) as a clear oil: $[\alpha]^{25}_{D}$ −10.0 (*c* 1.0, $CHCl_3$); IR (film) $\nu$ 3380, 1248, 1129, 1037 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H), 4.54 (t, $J$ = 4.9 Hz, 1H), 4.46 and 4.38 (AB, $J$ = 11.3 Hz, 2H), 3.85−3.25 (m, 4H, partially overlapped), 3.80 (s, 3H), 3.62 (br s, 2H), 3.35 (s, 3H), 3.28 (s, 3H), 2.45−2.16 (m, 2H), 1.98 (ddd, $J$ = 13.8, 8.0, 3.3 Hz, 1H), 1.73−1.75 (m, 1H), 1.42 (dd, $J$ = 14.5, 4.5 Hz, 1H), 0.89 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 159.6, 129.7 (2C), 129.2, 114.0 (2C), 102.5, 76.4, 73.2, 69.2, 67.1, 67.0, 65.7, 55.3 (2C), 53.2, 52.2, 44.2, 41.0, 39.5, 34.0, 25.9 (3C), 21.1, −4.1, −5.1. Anal. Calcd for $C_{27}H_{48}O_8Si$: C, 61.33; H, 9.15. Found: C, 61.18; H, 9.06.

**(1*S*,2*S*,3*S*,4*S*,6*R*)-1-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-(2,2-dimethoxyethyl)-3-methyl-7-oxabicyclo[4.2.0]octane-2-carbaldehyde (+)-1.** To an ice-cold stirred solution of (+)-**17** (70 mg, 0.15 mmol) in $CH_2Cl_2$ (5 mL) were added powdered 4 Å molecular sieves (1 g) then *N*-methylmorpholine *N*-oxide (34 mg, 0.29 mmol, 2.0 equiv) followed by a catalytic amount of TPAP. The deep green solution was stirred at rt under argon for 1 h and poured into aqueous $Na_2SO_3$. After extraction with ether, the organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by column chromatography gave (+)-**1** (54 mg, 78%) as a clear oil: $[\alpha]^{25}_{D}$ +9.2 (*c* 1.0, $CHCl_3$); $[\alpha]^{20}_{D}$ lit.[9] +9.4 (*c* 0.5, $CHCl_3$); IR (film) $\nu$ 2848, 2799, 1712, 1088 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.99 (d, $J$ = 2.6 Hz, 1H), 7.35−7.28 (m, 5H), 4.94 (br dd, $J$ = 7.7, 2.5 Hz, 1H), 4.66 and 4.55 (AB, $J$ = 7.8 Hz, 2H), 4.57 and 4.46 (AB, $J$ = 11.4 Hz, 2H), 4.50 (AB*X*, $J$ = 6.0, 4.6 Hz, 1H), 3.73 (dd, $J$ = 6.3, 4.9 Hz, 1H), 3.25 (s, 3H), 3.24 (s, 3H), 2.96 (d, $J$ = 2.6 Hz, 1H), 2.23 (ddd, $J$ = 15.4, 7.7, 4.9 Hz, 1H), 1.98 (ddd, $J$ = 15.4, 6.3, 2.5 Hz, 1H), 1.77 and 1.70 (*AB*X, $J$ = 14.4, 6.0, 4.6 Hz, 2H), 1.20 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 203.9, 138.0, 128.4 (2C), 127.6, 127.4 (2C), 101.9, 83.1, 77.4, 76.0, 71.7, 65.5, 56.7, 52.8, 52.4, 39.6, 39.4, 34.1, 25.8 (3C), 19.2, 18.1, −4.0, −4.9. Anal. Calcd for $C_{26}H_{42}O_6Si$: C, 65.24; H, 8.84. Found: C, 64.99; H, 8.81. HRMS (ESI) calcd for $C_{26}H_{46}N_1O_6Si_1$: 496.3088 [M + $NH_4^+$]; found 496.3090.

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**Supporting Information Available:** Additional experimental procedures and spectroscopic data for (+)-**4**−(+)-**9** and **12**−(+)-**17**; copies of $^1H$ and $^{13}C$ NMR spectra for all compounds and NOESY experiments for (+)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The starting material in Danishefsky's strategy is the useful synthon (*S*)-Wieland-Miescher ketone. (*S*)-W.-M. ketone is commercially available but very expensive. The cost exhibits the difficulty of the experimental technique to obtain enantiopure W.-M. ketone. Indeed, this is not a trivial manipulation to obtain a large amount of this enantiopure derivative efficiently, and this remains difficult. The most direct and practical method seems to be the asymmetric Robinson annulation of a precursor with proline followed by repeated recrystallizations (Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. VII, pp 368−372). See also: Kasai, Y.; Shimanuki, K.; Kuwahara, S.; Watanabe, M.; Harada, N. *Chirality* **2006**, *18*, 177–187.