# Total Synthesis of (±)-Scopadulin

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The first total synthesis of (±)-scopadulin, an aphidicolane diterpene, is described. The core structure (A/B/C/D ring system) was constructed by an initial synthesis of the B/C/D ring system by our reported methods and a subsequent A ring cyclization by intramolecular aldol condensation. A highly stereoselective cyanation of the tetracyclic enone by $Et_2AlCN$ gave a *trans*-fused A/B ring system with a *β*-cyanide at C-4. Stereoselective construction of a quaternary carbon at C-4 was achieved by α-alkylation of the cyano group and conversion of the sterically hindered cyano group to a methyl group via our novel reaction for conversion of primary aliphatic amines into alcohols. Finally, the total synthesis of (±)-scopadulin was accomplished by a highly chemo- and stereoselective methylation at C-16 and modification of the C-4 α-functionality. The stereoselectivity observed in the $MeTi(O\text{-}i\text{-}Pr)_3$-mediated methylation for the generation of a tertiary axial alcohol at C-16 is extremely high.

## Introduction

The widely distributed plant *Scoparia dulcis* (fam. Scrophulariaceae) has long been used as a traditional medicine in Paraguay, India, and Taiwan for hypertension, toothaches, blennorhagia and stomach disorders.[1] Due to these diverse medicinal properties, considerable phytochemical investigations were carried out on this plant by different groups to identify the active constituents. Hayashi and co-workers isolated and characterized a number of structurally unique tetracyclic diterpenoids (scopadulane diterpenes), exemplified by scopadulcic acid A (**1**), scopadulcic acid B (**2**), and scopadulciol (**3**) (Figure 1) from the Paraguayan crude drug Typchá-Kuratû prepared from the whole plants of *S. dulcis*.[2] Scopadulciol has also been isolated earlier from a Bangladeshi collection of *S. dulcis*.[3] The continued investigation of Hayashi's group on this plant resulted in isolation and characterization of a novel tetracyclic aphidicolane diterpenoid scopadulin (**4**) in 1990 (Figure 1).[4] This is the first example of an aphidicolane diterpenoid from a higher plant. The structure of scopadulin was determined by spectroscopic studies and finally confirmed by single-crystal X-ray crystallography of its acetone solvate.[4]

The synthetically challenging structural complexity of scopadulin due to the presence of four quaternary carbons and eight stereocenters coupled with its notable antiviral and cytotoxic activities[4] has attracted the organic chemists as a worthy synthetic target. Like other aphidicolane[5] and stemodane[6] diterpenes, scopadulin has a similar bicyclo[3.2.1]octane moiety (C/D ring system) fused with a *trans*-decalin moiety (A/B ring system). In addition, the presence of two adjacent quaternary carbon centers at C-9 and C-10 makes these diterpenes quite crowded. Although numerous synthetic pathways for other aphidicolane[7] and stemodane[7b,8] diterpenes and, recently, the total synthesis of scopadulcic acid A (**1**),[9] scopadulcic acid B (**2**),[9b,10] and scopadulciol (**3**)[9b] were established, no synthetic approach toward scopadulin (**4**) has been reported to date. Previously, successful syntheses of

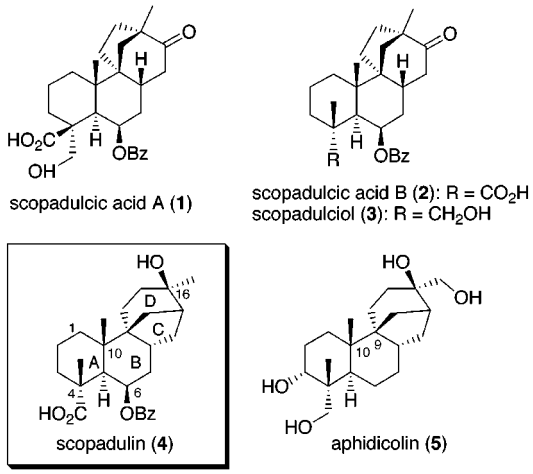


**Figure 1.**

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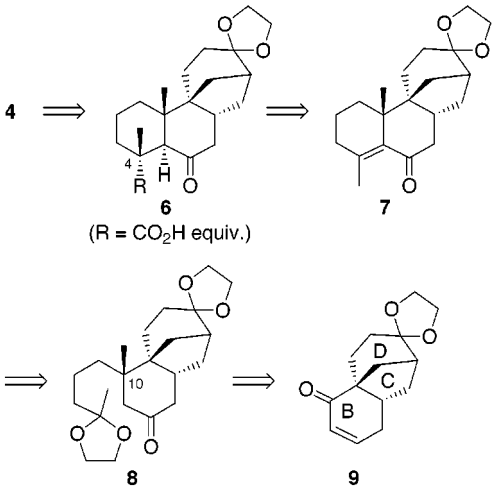
aphidicolin (**5**)[11] and stemodinone[8f] were established in our laboratory. Our continued interest in this diterpene family prompted us to target the total synthesis of this novel diterpene.

Although we started our project for the total synthesis of scopadulin some years ago, the progress in the synthetic study was hampered due to several failed attempts to construct the A/B ring system with the requisite stereochemistry. We encountered many difficulties in the stereoselective generation of a quaternary carbon at C-4 and subsequent manipulation of the hindered functionalities. Accordingly, the problems associated with the total synthesis were successfully overcome by conducting a model study for the stereoselective construction of the A/B ring system with the desired functionalities.[12] In the course of the model study, we discovered a novel and efficient one-step conversion of primary aliphatic amines into alcohols.[12a] In this paper, we describe the total synthesis of (±)-scopadulin in full details,[13] utilizing our novel reaction.

**Scheme 1**




## Results and Discussion

**Initial Synthetic Approach.** Our synthetic studies on scopadulin were based on a strategy of construction of the B/C/D ring system followed by A ring cyclization. Therefore, we planned to start from the B/C/D analogue **9** whose synthesis was previously reported from our laboratory.[11] As shown in Scheme 1, we thought that scopadulin (**4**) might be synthesized by functional group modifications of the tetracyclic precursor **6,** which could be accessed from the enone **7** by stereoselective generation of a quaternary carbon at C-4 with a carboxyl equivalent. We envisaged that an angular methyl group would provide the requisite stereochemical features. The tetracyclic enone **7**, which is regarded as the core structure, might be easily obtained by aldol condensation from **8**, which was assumed to be obtained from **9** in a straightforward manner. We anticipated that the facial bias provided by the bicyclooctane moiety (C/D ring system) would favor the stereoselective introduction of a methyl group at C-10.

Starting from **9**, we initially synthesized the scopadulin core structure as depicted in Scheme 2. Barbier reaction of **9** with 2-(3-chloropropyl)-2-methyl-1,3-dioxolane afforded the allyl alcohol **10** in excellent yield. Dauben−Michno oxidative rearrangement[14] of **10** provided the transposed enone **11**. Conjugate addition of $Me_2CuLi$ to the enone **11** gave the ketone **8** in excellent yield. $\beta$-Face addition of a methyl group proceeded exclusively because the α-side was more congested due to the presence of a bicyclooctane moiety (structure **11** within brackets). Deketalization of **8** gave the triketone **12**, which was cyclized quantitatively by acid-catalyzed intramolecular aldol condensation to yield the enone **13**.[15] Selective ketalization proceeded smoothly and efficiently to provide **7** in nearly quantitative yield.

Our next operation was the stereoselective formation of a quaternary carbon at C-4. We assumed that the angular methyl group at C-10 would favor α-face addition of a cyano nucleophile to the enone **7** to give the desired nitrile **14** (Scheme 3), which could be easily transformed to scopadulin by modification of functional groups. How-

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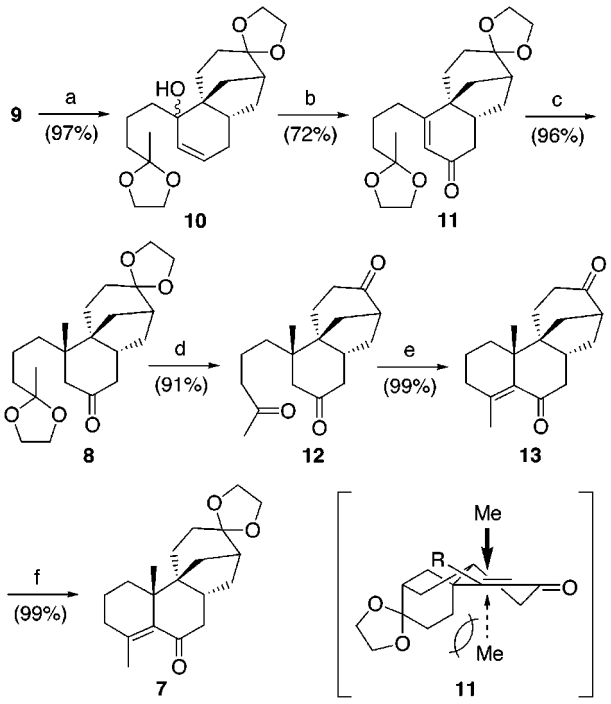
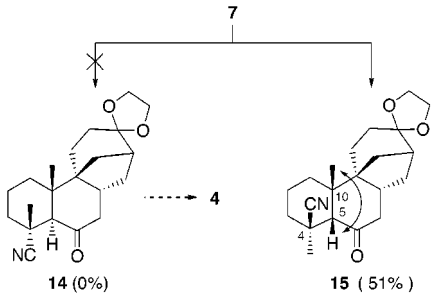
(15) One-step conversion of **8** into **13** by deketalization and a subsequent aldol condensation was quite difficult. For example, treatment of **8** with *p*-TSA in benzene under reflux (Dean−Stark) led to a complex mixture of unidentified compounds.

**Scheme 2**[a]




[a] Reaction conditions: (a) Li, 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, $Et_2O$, ultrasound, rt; (b) PCC, AcONa, Celite, $C_6H_6$; (c) $Me_2CuLi$, $Et_2O$, −20 to 0 °C; (d) PPTS, $H_2O$, acetone; (e) *p*-TSA, $C_6H_6$, reflux (Dean−Stark); (f) $(CH_2OH)_2$, PPTS, $C_6H_6$, reflux (Dean−Stark).

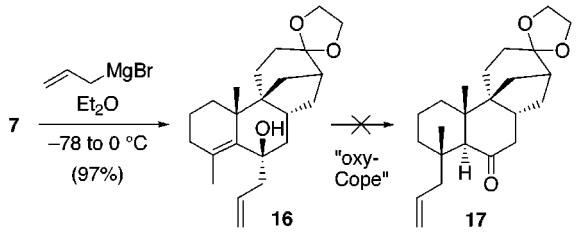
**Scheme 3**[a]



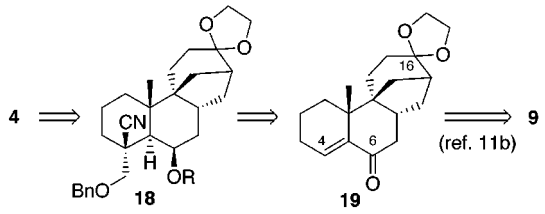

[a] Reaction conditions: $Et_2AlCN$, $C_6H_6$, 0 °C.

ever, conjugate addition of $Et_2AlCN$ to the enone **7** afforded the undesired adduct **15**. Not only did the CN addition occur from the *β*-face, the A/B ring junction moreover was the cis configuration. The stereochemistries were determined by NOE analyses. NOE was observed between 10-$CH_3$ and 5-H (4%). However, no NOE was found between 4-$CH_3$/5-H and 4-$CH_3$/10-$CH_3$. The stereoelectronic effects coupled with the fact that the CN group is sterically very small and was not disturbed by the axial methyl group favored this undesired addition. Moreover, Nagata reported that CN addition would occur in an axial fashion.[16] And possibly the presence of the C-4 methyl group at the α-face of the enolate intermediate encouraged protonation from the less hindered *β*-face resulting in the *cis*-fused A/B ring system. Copper-catalyzed conjugate addition of a relatively bulkier reagent (allylmagnesium bromide[17] or methoxyallyl-

**Scheme 4**




**Scheme 5**




copper[18]) to the enone **7** was investigated. However, the reactions were unrewarding in both cases. Thus, we learned that the formation of a quaternary carbon at C-4 via the conjugate addition was extremely difficult presumably due to the steric hindrance exerted by the methyl groups at both C-4 and C-10.

Next, a different strategy via the anionic oxy-Cope rearrangement[19] was applied to the stereoselective generation of a quaternary carbon at C-4. As shown in Scheme 4, 1,2-addition of allylmagnesium bromide to the enone **7** gave the homoallyl alcohol **16** in excellent yield.[20] Then, some oxy-Cope conditions (KH, KH/18-crown-6, KHMDS, KHMDS/18-crown-6, $Pd(OAc)_2$, etc.) were examined.[21] However, the desired product **17** was not formed in any case. Possibly, steric hindrance due to the presence of the methyl substituent at C-4 and/or conformational unbias of the quasi-equatorial pendant allyl substituent at C-6 are the causes for these unsuccessful results.

**Revised Synthetic Plan.** The presence of a methyl substituent at C-4 impeded the stereoselective formation of a quaternary carbon at C-4. Therefore, we changed our strategy and planned a different route via the enone **19**, which lacks a methyl substituent at C-4 (Scheme 5). Synthesis of **19** from **9** was previously reported from our laboratory[11b] (see the Supporting Information for the augmented and updated data for **19** and the intermediates). Conjugate addition of $Et_2AlCN$ to the enone **19** might proceed smoothly as learned from the previous discussion. We envisaged that scopadulin could be syn-

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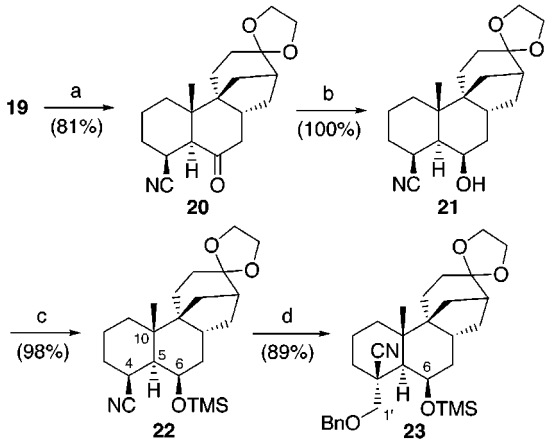
(20) Stereochemistry of **16** was deduced by NOE analysis: no NOE was observed between allylic protons and axial 10-methyl protons.
(21) (a) Evans, D. A.; Golob, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, 2559. (c) Evans, D. A.; Baillargeon, W. A. *Tetrahedron Lett.* **1978**, 3319. (d) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (e) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865. (f) Overman, L. E.; Jacobson, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225. (g) Overman, L. E. Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 1157.; *J. Am. Chem. Soc.* **1990**, *112*, 3945. (h) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

**Scheme 6**[a]




[a] Reaction conditions: (a) $Et_2AlCN$, TMSCl, $C_6H_6$, 0 °C; (b) $NaBH_4$, MeOH−THF (7:5), 0 °C; (c) TMSCl, pyridine, DMAP, $CH_2Cl_2$, 0 °C; (d) LDA, BOMCl, THF, −78 to 0 °C.

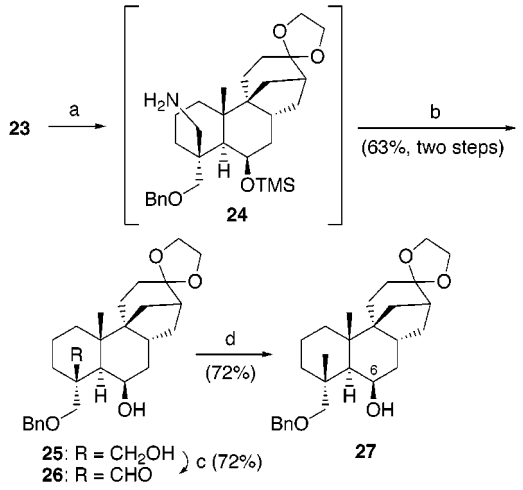
thesized by stereoselective generation of a quaternary carbon at C-4 with a carboxylic acid equivalent such as a benzyloxymethyl group and subsequent modification of functional groups at the C-4, C-6, and C-16 positions. The difficulties associated with the formation of a quaternary carbon at C-4 and manipulation of the hindered functionalities were overcome by a model study.[12]

**Stereoselective Construction of a Quaternary Carbon at C-4**. The tetracyclic enone **19** was synthesized by a procedure similar to that reported from our laboratory.[11b] To generate a quaternary carbon at C-4, a convenient strategy reported by Overman and co-workers was followed.[9a,c] Conjugate addition of $Et_2AlCN$ to **19** in the presence of TMSCl proceeded smoothly and stereoselectively to give the nitrile **20** as a single isomer. Borohydride reduction of **20** and trimethylsilyl protection of the resulting secondary alcohol **21** furnished the silyl ether **22** with the requisite stereochemistry, in nearly quantitative yield (Scheme 6).

The stereochemistry of **22** was confirmed by NOE analysis. Irradiation of the signal of 4-H led to NOE enhancement of the signals of 5-H and 6-H. In contrast, NOE was absent in 4-H, 5-H, or 6-H when 10-methyl was irradiated. The nitrile **22** was then alkylated with LDA/BOMCl to provide **23** having a quaternary carbon at C-4 with the desired stereochemistry. The stereochemistry was confirmed by NOE analyses. Strong NOE was observed between 6-H and 1′H. The facial selectivity was regulated by the axial methyl at C-10 and a trimethylsiloxy group at C-6.[9a,c]

**Conversion of the Hindered Cyano Group to a Methyl Group via our Novel Amine-to-Alcohol Reaction**. Unlike the model study,[12] without deprotecting the TMS group, the nitrile **23** was exposed to excess $LiAlH_4$ at reflux, and the resulting crude amine was subjected to the novel reaction conditions (KOH, diethylene glycol, 210 °C) for the one-step direct conversion of primary aliphatic amines into alcohols[12a,22] to give the diol **25** in 63% yield in two steps (Scheme 7). This simultaneous TMS deprotection by the base-mediated reaction saved one step and provided better overall yield than that of the model study. Moreover, purification of the intermediate amine was not necessary for the efficient synthesis which greatly simplified the operation. This conversion further clarified the applicability of the novel reaction to a sterically hindered functionality in a complex molecule. Selective oxidation of the primary alcohol of **25** with $RuCl_2(PPh_3)_3$[23] in the presence of air[24] afforded the aldehyde **26** (72%) together with recovered starting material (21%). The aldehyde **26** was then converted to the 4,10-dimethylated alcohol **27** by Huang−Minlon reduction.[25]

**Scheme 7**




[a] Reaction conditions: (a) $LiAlH_4$, THF, 75 °C; (b) KOH, diethylene glycol, 210 °C; (c) $RuCl_2(PPh_3)_3$, $C_6H_6$, air, room temperature; (d) $NH_2-NH_2{\cdot}H_2O$, $K_2CO_3$, diethylene glycol, 170−210 °C.

**Benzoylation of the Hindered Secondary Alcohol at C-6**. We previously investigated the benzoylation of the highly congested secondary hydroxyl group at C-6 in our model study,[12b] and we found that benzoylation was quite difficult and BzOTf[26]−2,6-lutidine was the reagent of choice. The same reagent was used for **27**. However, the presence of a ketal functionality at C-16 resulted in the formation of several unidentified, undesired side products along with the desired benzoate **28** (Scheme 8) and a large amount of the starting material. This undesired product formation occurred due to the electrophilic nature of BzOTf. When BzOTf was added very slowly by a micropipet to a well-stirred mixture of **27** and 2,6-lutidine, the formation of undesired products decreased substantially and the reaction mainly contained **28** (37%), the starting alcohol (44%), and traces of the side products **29** and **30**.[27] The recovered starting mate-

(22) We conducted the labeling experiment using a simple amine and ethylene glycol-$d_6$. According to the $^1H$ NMR spectra of the resulting alcohol, a considerable amount of the carbinol protons was deuterated, which implies that a redox mechanism (imine formation, hydrolysis, and reduction) would be one of the reaction pathways. We are now undertaking a detailed study of these reactions, which will be reported elsewhere. We thank the reviewer who suggested necessity of the labeling experiment.

(23) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

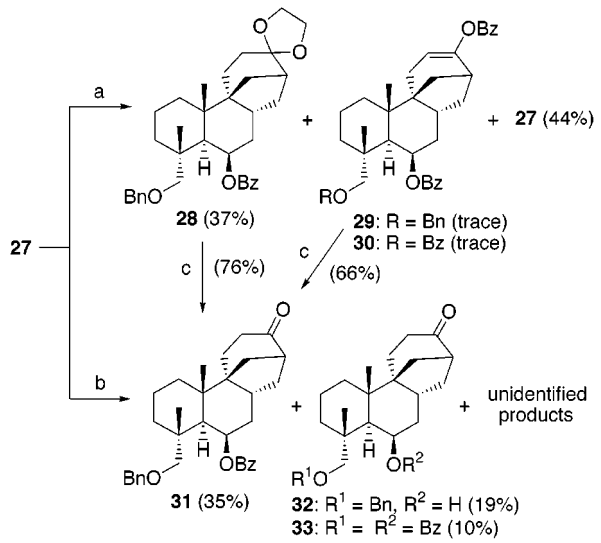
(24) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohsima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830.

(25) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487. (b) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301. In this reduction, no deformylated product was detected in the reaction mixture.

(26) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875.

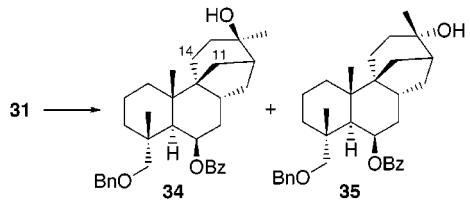
(27) This decreased formation of the side products might be due to sufficient formation of the less reactive BzOTf−lutidine complex resulting in a low concentration of free BzOTf (as the rate of complexation between BzOTf and 2,6-lutidine is faster than the Lewis acidic behavior to the ketal functionality).[26]

**Scheme 8**[a]




[a] Reaction conditions: (a) BzOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C; (b) BzOTf, $CH_2Cl_2$, −78 °C; (c) dilute HCl, MeOH, 40 °C.

**Scheme 9**




rial was recycled. Employment of BzOTf alone to **27** furnished a number of side products with the desired ketone **31**, and the starting material disappeared within a few minutes. The benzyl group was mildly susceptible to BzOTf, and debenzylation and subsequent benzoylation of the resulting primary alcohol commenced to give the bis-benzoate **33**.[28] The benzoate **28** and the enolate **29** were successfully transformed to the ketone **31** by treatment with a dilute acid.

**Chemo- and Stereoselective Methylation at C-16 and Completion of the First Total Synthesis of (±)-Scopadulin.** Completion of the total synthesis from **31** further required a chemo- and stereoselective methylation at the C-16 ketone and modification of the C-4 α-substituent. The tertiary hydroxyl group at C-16 of scopadulin is located in an axial position. Therefore, a methylating reagent that predominantly attacks from the equatorial side would be suitable for the reaction, provided that the reagent should be inert enough to the ester functionality at C-6. Initially, the reaction was conducted with methyllithium to identify the two isomers. Treatment of **31** with methyllithium at −78 °C afforded two chromatographically separable isomeric alcohols **34** and **35** (Scheme 9 and Table 1) in nearly equivalent ratio (54:46) along with traces of unidentified product(s), possibly debenzoylated isomer(s). According to the NMR spectra in $CDCl_3$ of the isolated isomers, the less polar isomer showed a methyl singlet at $\delta$ 1.14 that is 0.15 ppm more upfield than that of the more polar isomer ($\delta$ 1.29).[29]

**Table 1. Chemo- and Stereoselective Methylation of 31**

| entry | conditions | yield (%) | ratio[c] **34**:**35** |
|---|---|---|---|
| 1 | MeLi, −78 °C, 20 min | 80[a,b] | 54:46[b] |
| 2 | MeLi−$LiClO_4$, −65 °C, 2 h | 24[c] | 50:50 |
| 3 | MeTi(O-*i*-Pr)$_3$, rt, 18 h | 66[c] | >99:1 |

[a] Isolated yield. [b] Trace amount of debenzoylated product was detected. [c] Determined by $^1$H NMR spectra (500 MHz).

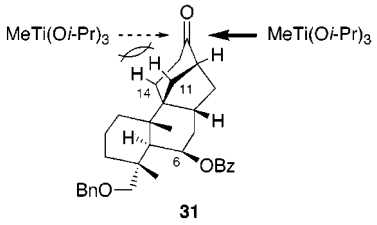



**Figure 2.** Stereoselective methylation of **31**.

Next, the selective formation of **34** was investigated by some reagents that essentially prefer equatorial attack. Among the reported reagents, we selected MeLi−$LiClO_4$ and MeTi(O-*i*-Pr)$_3$ for our investigation.[30] Reaction of MeLi−$LiClO_4$[31a] with the ketone **31** was sluggish and was not selective (Table 1, entry 2). However, when **31** was allowed to react with an excess of MeTi(O-*i*-Pr)$_3$[31c,d,32] at room temperature, the desired alcohol **34** was formed exclusively (>99:1). This exclusive equatorial addition occurred due to the steric repulsion of the bulky reagent with the axial hydrogens at both C-11 and C-14 (Figure 2).[33] In contrast, reaction with MeLi−$LiClO_4$ was not selective, probably due to lack of complex formation of the ketone with $LiClO_4$.[34]

As shown in Scheme 10, debenzylation of **34** afforded the diol **36** in excellent yield. Oxidation of the primary alcohol to a carboxyl group was performed by $RuO_4$[35,36] to give (±)-scopadulin (**4**) in 63% yield. This synthetic (±)-scopadulin was in all respects (500 MHz $^1$H NMR

(28) By taking the advantage of the Lewis acidic nature of BzOTf, Brown and Koreeda[26] succeeded in the conversion of a steroidal alcohol having a ketal functionality to the corresponding keto benzoate in 85% yield in one step using three equivalents of BzOTf. Formation of the undesired side products in our case might result from the steric demand of the C-6 OH as well as the susceptibility of the benzyl group to BzOTf.

(29) The desired and the undesired isomers were identified by converting both isomers separately into the corresponding 4-carboxylic acid derivatives **4** and **38** (Scheme 10), and it was confirmed that the less polar isomer was the desired product **34**.

(30) Although several reagents were used for the selective equatorial attack to generate an axial tertiary alcohol,[8a,31] MeLi−$LiClO_4$,[31a] and MeTi(O-*i*-Pr)$_3$[31c,d] were sorted out considering the chemo- and stereoselectivities factors. Although MeLi−$Me_2CuLi$[31b] was also reported to display good stereoselectivity, this reagent was more active than MeLi and might be reactive with the ester functionality.

(31) (a) Ashby, E. C.; Nodling, S. A. *J. Org. Chem.* **1979**, *44*, 4371. (b) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. (c) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (d) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441.

(32) This reagent was freshly prepared and purified by distillation (50−53 °C/0.01 Torr) prior to use by a reported method.[31d]

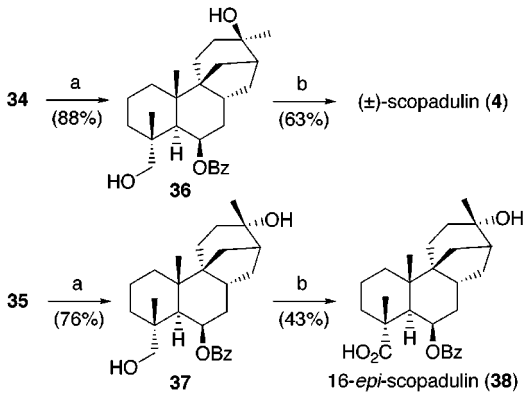
(33) Only the less polar desired isomer was detected by TLC and $^1$H NMR spectrum. Piers and co-workers observed a 6:1 selectivity on the methylation of a stemodin precursor with MeTi(O-*i*-Pr)$_3$.[8b] Our surprisingly high selectivity would be attributed to the axial benzoyloxy group at C-6, which will affect the conformation of the B/C/D ring system.

(34) The selectivity of the reaction of ketone by MeLi−$LiClO_4$ is regulated by the efficiency of complex formation of the ketone with $LiClO_4$.[31a] Usually, unhindered ketone gives good result due to sufficient complex formation.

(35) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(36) We preferred $RuO_4$ instead of the Jones reagent which was used in the model study[12] because we surmised that the highly acidic nature of the Jones reagent might cause elimination of the tertiary alcohol at C-16.

**Scheme 10**[a]




[a] Reaction conditions: (a) Pd/C, $H_2$, MeOH, rt; (b) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $CCl_4$, $CH_3CN$, $H_2O$, rt.

(pyridine-$d_5$), 125 MHz $^{13}C$ NMR (pyridine-$d_5$), IR, and TLC mobility in three solvent systems), indistinguishable from an authentic sample of the natural scopadulin supplied by Professor Hayashi.[4]

The more polar undesired isomer **35** was similarly converted to the 16-epimer of scopadulin (**38**),[37] which showed marked differences in $^1H$ NMR (500 MHz, pyridine-$d_5$) spectra from those of natural and synthetic scopadulin. The axial methyl at C-16 resonated at $\delta$ 1.50, whereas the equatorial methyls at C-16 of the natural and synthesized scopadulin both resonated at $\delta$ 1.29. Some other proton signals also differ from those of scopadulin (also see and compare the data of **4** and **38** in the Experimental Section).

## Conclusion

We have accomplished the first total synthesis of (±)-scopadulin. The strategic elements of this synthesis are as follows: (1) the B/C/D-fused A-ring cyclization, (2) conversion of the hindered cyano group to a methyl group via our novel reaction, and (3) a highly chemo- and stereoselective methylation at C-16 by $MeTi(O\text{-}i\text{-}Pr)_3$. Moreover, during the synthetic studies, the problems associated with the stereoselective construction of the C-4 quaternary carbon with the methyl-substituted enone **7** were identified and overcome by changing the strategy. In addition, the synthetic utility of our novel reaction for the one-step conversion of primary aliphatic amines into primary alcohols in a complex molecule was clarified by this total synthesis. Total yield of (±)-scopadulin starting from commercially available 1,4-cyclohexadione is 0.29% in 29 steps. Biological screening and the structure−activity relationship of some of the synthetic intermediates and the debenzylated derivatives[38] of the C-4 benzyloxymethyl substituent are now being investigated in collaboration with Professor Hayashi.

## Experimental Section

**General Methods.** Unless otherwise specified, all reactions were carried out in well-dried glassware, using an $N_2$ atmosphere. THF and $Et_2O$ were distilled from sodium benzophenone ketyl under $N_2$. MeOH was distilled from Mg. $CH_2Cl_2$, benzene, *n*-hexane, diisopropylamine, triethylamine, and pyridine were distilled from $CaH_2$ under $N_2$. BOMCl was distilled over $CaCl_2$. Other solvents were used without further purification. Melting points are uncorrected. 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, td = triple doublet, 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.

**(±)-(1*S**,6*S**,8*R**)-2-[3-(2-Methyl-1,3-dioxolan-2-yl)-propyl]tricyclo[6.3.1.0$^{1,6}$]dodec-3-en-2-ol-9-one 9,9-Ethylene Acetal (10).** An Li dispersion (30%; 475 mg, 20.4 mmol), washed with dry hexane, was suspended in THF (25 mL) under an argon atmosphere. The enone **9** (753 mg, 3.22 mmol) and 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (2.51 mL, 16.1 mmol) were added. The mixture was sonicated for 30 min on an ultrasonic bath at room temperature. 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 1.13 g (97%) of **10** as a colorless solid. Mp: 99−101 °C (*n*-hexane/EtOAc). IR (KBr) $cm^{-1}$: 3590, 1635, 1115. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.32 (s, 3H), 1.35−1.96 (m, 16H), 2.01−2.06 (m, 1H), 2.11−2.19 (m, 2H), 3.82−4.00 (m, 8H), 5.46 (d, $J$ = 10.5 Hz, 1H), 5.73 (ddd, $J$ = 10.5, 5.0, 2.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.5, 23.7, 25.6, 28.3, 30.5 (2C), 34.8, 38.1, 39.7, 39.8, 43.0, 47.3, 63.9, 64.5 (2C), 64.6, 76.5, 110.1, 111.8, 128.6, 133.1. MS (FAB) *m*/*z*: 365 ($MH^+$, 100). HRMS (FAB): calcd for $C_{21}H_{33}O_5$ ($MH^+$) 365.2328, found 365.2314.

**(±)-(1*S**,6*R**,8*R**)-2-[3-(2-Methyl-1,3-dioxolan-2-yl)-propyl]tricyclo[6.3.1.0$^{1,6}$]dodec-2-ene-4,9-dione 9,9-Ethylene Acetal (11).** To a stirred suspension of PCC (1.34 g, 6.20 mmol), AcONa (250 mg, 3.10 mmol), and Celite (1.0 g) in $CH_2Cl_2$ (26 mL) was added a solution of the alcohol **10** (1.13 g, 3.10 mmol) in $CH_2Cl_2$ (14 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. $Et_2O$ (30 mL) was added, and the suspension was applied to a Florisil column and eluted with $Et_2O$. The eluate was concentrated and the residue was purified by column chromatography (1:1 hexane/EtOAc) to give **11** (810 mg, 72%) as a colorless oil. IR (KBr) $cm^{-1}$: 1662, 1605, 1115. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.31 (s, 3H), 1.48−1.69 (m, 8H), 1.81−1.93 (m, 2H), 1.96−2.03 (m, 1H), 2.12 (d, $J$ = 11.5 Hz, 1H), 2.25−2.32 (m, 3H), 2.33−2.41 (m, 2H), 2.58−2.66 (m, 1H), 3.83−4.02 (m, 8H), 5.70 (s, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 20.9, 23.8, 29.6, 30.6, 31.7, 32.6, 36.8, 38.7, 39.6, 42.7, 44.7, 46.8, 64.0, 64.6 (3C), 109.7, 110.8, 124.5, 173.0, 201.0. MS (EI) *m*/*z*: 362 ($M^+$, 13.0), 99 (100). HRMS (EI): calcd for $C_{21}H_{30}O_5$ 362.2093, found 362.2100.

**(±)-(1*S**,2*S**,6*R**,8*R**)-2-Methyl-2-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]tricyclo[6.3.1.0$^{1,6}$]dodecane-4,9-dione 9,9-Ethylene Acetal (8).** To a stirred suspension of CuI (853 mg, 4.48 mmol) in $Et_2O$ (17 mL) was added dropwise MeLi (1.16 M in $Et_2O$; 7.7 mL, 8.93 mmol) at −20 °C, and the mixture was stirred for 15 min. A solution of the enone **11** (810 mg, 2.24 mmol) in $Et_2O$ (3 mL) was then added dropwise at −20 °C, and the reaction mixture was warmed to 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was neutralized by aqueous $NH_4Cl$. The whole was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the concentrate by a column chromatography (1:2 hexane/EtOAc) afforded **8** (815 mg, 96%) as a colorless oil. IR (KBr) $cm^{-1}$: 1700, 1111. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 0.96 (s, 3H), 1.24−1.34 (m, 2H), 1.31 (s, 3H), 1.36−1.44 (m, 3H), 1.50−1.66 (m, 4H), 1.80−1.88 (m, 4H), 1.90−1.95 (m, 1H), 2.12 (d, $J$ = 16.0 Hz, 1H), 2.21 (t, $J$ = 7.0 Hz, 1H), 2.29−2.45 (m, 4H), 3.82−4.01 (m, 8H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.7, 20.1, 23.9, 26.0, 29.7, 29.9, 35.3, 39.7, 40.0, 40.1, 40.2, 42.9, 43.6, 46.3, 51.1, 64.0, 64.7 (3C), 109.9, 111.3,

(37) We suffered a low yield (43%) in the oxidation of **37** into 16-*epi*-scopadulin **38**. However, we could not optimize the reaction conditions due to a small amount of **37**.

(38) Free hydroxyl groups at this position are known to be responsible for the binding in the host cavity. See: McMurry, J. E.; Webb, T. R. *J. Med. Chem.* **1984**, *27*, 1367.

211.4. MS (EI) *m*/*z*: 378 ($M^+$, 0.4), 99 (100). HRMS (EI): calcd for $C_{22}H_{34}O_5$ 378.2406, found 378.2416.

**(±)-(1*S**,2*S**,6*R**,8*R**)-2-Methyl-2-(4-oxopentyl]tricyclo-[6.3.1.0$^{1,6}$]dodecane-4,9-dione (12).** Pyridinium *p*-toluenesulfonate (PPTS) (25 mg, 0.099 mmol) and $H_2O$ (0.03 mL) were added to a solution of the ketone **8** (149 mg, 0.53 mmol) in acetone (6 mL), and the resulting mixture was refluxed for 4 h. Saturated $NaHCO_3$ (few drops) was added, and acetone was evaporated. The residue was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the concentrate by column chromatography (1:2 hexane/EtOAc) yielded **12** (104 mg, 91%) as a colorless solid. Mp: 112−113 °C (*n*-hexane/EtOAc). IR (KBr) $cm^{-1}$: 1720 (br). $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.04 (s, 3H), 1.21−1.26 (m, 1H), 1.33 (dd, $J$ = 14.5, 9.0 Hz, 1H), 1.43−1.63 (m, 3H), 1.85−1.94 (m, 2H), 2.07 (dd, $J$ = 9.0, 5.5 Hz, 2H), 2.14 (s, 3H), 2.17−2.21 (m, 2H), 2.35 (dt, $J$ = 15.5, 6.5 Hz, 2H), 2.41−2.44 (m, 3H), 2.51−2.64 (m, 3H), 2.78 (t, $J$ = 6.5 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.4, 20.1, 25.1, 30.0, 30.8, 34.0, 36.8, 39.5, 40.2, 41.2, 42.6, 43.9, 47.0, 49.4, 51.1, 208.1, 209.9, 213.1. MS (EI) *m*/*z*: 290 ($M^+$, 18.7), 209 (100). HRMS (EI): calcd for $C_{18}H_{26}O_3$ 290.1879, found 290.1878.

**(±)-(1*S**,2*R**,10*R**,12*R**)-2,6-Dimethyltetracyclo-[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-6-ene-8,13-dione (13).** To a solution of **12** (314 mg, 1.08 mmol) in benzene (15 mL) was added *p*-toluenesulfonic acid monohydrate (*p*-TSA) (21 mg, 0.11 mmol), and the resulting mixture was refluxed for 6 h (Dean−Stark device). Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by a column chromatography (2:3 hexane/EtOAc) to provide the enone **13** (294 mg, 99%) as a colorless solid. Recrystallization from *n*-hexane/acetone gave analytically pure **13** as a colorless solid. Mp: 150−151 °C. IR (KBr) $cm^{-1}$: 1716, 1678, 1614. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.07 (s, 3H), 1.34 (dd, $J$ = 14.0, 8.0 Hz, 1H), 1.37−1.41 (m, 1H), 1.60−1.68 (m, 2H), 1.74 (d, $J$ = 12.0 Hz, 1H), 1.77−1.87 (m, 2H), 1.83 (s, 3H), 1.91 (ddd, $J$ = 12.0, 6.0, 3.0 Hz, 1H), 1.97−2.13 (m, 3H), 2.20−2.33 (m, 2H), 2.38−2.43 (m, 1H), 2.49−2.55 (m, 1H), 2.65−2.70 (m, 2H), 2.78 (t, $J$ = 6.5 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 18.5, 22.2, 22.5, 24.9, 30.8, 31.5, 33.4, 34.3, 34.8, 38.7, 40.8, 43.8, 47.7, 49.1, 137.1, 144.5, 203.7, 213.9. MS (EI) *m*/*z*: 272 ($M^+$, 61), 257 (100). HRMS (EI): calcd for $C_{18}H_{24}O_2$ 272.1777, found 272.1787.

**(±)-(1*S**,2*R**,10*R**,12*R**)-2,6-Dimethyltetracyclo-[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-6-ene-8,13-dione 13,13-Ethylene Acetal (7).** To a solution of the ketone **13** (18 mg, 0.066 mmol) in benzene (1.2 mL) were added PPTS (2.5 mg, 0.01 mmol) and ethylene glycol (2 drops), and the mixture was refluxed (Dean−Stark device) at 110 °C for 3 h. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried ($MgSO_4$), and concentrated. Purification of the concentrate by column chromatography (3:1 hexane/EtOAc) afforded **7** (21 mg, 99%) as a colorless solid. Recrystallization provided colorless crystals. Mp: 180−181 °C (*n*-hexane/$CH_2Cl_2$). IR (KBr) $cm^{-1}$: 1682, 1117. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.01 (s, 3H), 1.25−1.33 (m, 3H), 1.38 (dd, $J$ = 13.5, 7.0 Hz, 1H), 1.56−2.09 (m, 10H), 1.80 (s, 3H), 2.23 (t, $J$ = 6.0 Hz, 1H), 2.34 (t, $J$ = 14.5 Hz, 1H), 2.45−2.60 (m, 2H), 3.83−4.01 (m, 4H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.7, 22.2 (2C), 26.7, 29.8, 30.4, 30.6, 33.6, 34.4, 37.3, 41.1, 43.6, 44.4, 46.8, 64.0, 64.6, 111.5, 138.2, 143.5, 204.7. MS (EI) *m*/*z*: 316 ($M^+$, 1.9), 99 (100). HRMS (EI): calcd for $C_{20}H_{28}O_3$ 316.2036, found 316.2035. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 8.88.

**(±)-(1*S**,2*S**,6*S**,7*R**,10*R**,12*R**)-2,6-Dimethyl-8,13-dioxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecane-6-carbonitrile 13,13-Ethylene Acetal (15).** A solution of the enone **7** (20 mg, 0.074 mmol) in benzene (0.37 mL) was added dropwise to a stirred solution of $Et_2AlCN$ (1.0 M in toluene; 0.22 mL, 0.22 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of saturated $NH_4Cl$ and warmed to room temperature. The resulting mixture was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by column chromatography (2:1 hexane/EtOAc) gave 13 mg (51%) of **15** as a colorless solid. Recrystallization (*n*-hexane/$CH_2Cl_2$) provided an analytically pure colorless solid. Mp: 132−133 °C. IR ($CHCl_3$) $cm^{-1}$: 2227, 1712, 1114. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.24−1.43 (m, 5H), 1.44 (s, 3H), 1.51 (s, 3H), 1.55−1.60 (m, 3H), 1.63−1.75 (m, 3H), 1.77−1.83 (m, 2H), 2.06 (ddd, $J$ = 14.0, 12.0, 8.0 Hz, 1H), 2.17−2.25 (m, 2H), 2.58 (dd, $J$ = 16.5, 8.0 Hz, 1H), 2.73−2.81 (m, 1H), 2.78 (s, 1H), 3.80−3.99 (m, 4H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.7, 19.8, 23.2, 26.1, 28.5, 30.2, 30.8, 33.5, 34.5, 36.8, 37.9, 42.2, 44.3, 45.7, 48.6, 56.7, 64.0, 64.6, 110.8, 126.8, 211.9. MS (EI) *m*/*z*: 343 ($M^+$, 13.7), 99 (100). HRMS (EI): calcd for $C_{21}H_{29}NO_3$ 343.2147, found 343.2163.

**(±)-(1*S**,2*S**,8*R**,10*R**,12*R**)-8-Allyl-2,6-dimethyl-teracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-6-en-8-ol 13,13-Ethylene Acetal (16).** Allylmagnesium bromide (1.0 M in $Et_2O$; 0.3 mL, 0.3 mmol) was added to a stirred solution of the enone **7** (10 mg, 0.030 mmol) in dry $Et_2O$ (1 mL) at −78 °C. The mixture was gradually warmed to 0 °C for 1 h. Saturated aqueous $NH_4Cl$ (excess) was added, and the resulting mixture was extracted with $Et_2O$, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The resulting concentrate was purified by column chromatography (3:1 hexane/EtOAc) to give 10 mg (97%) of **16** as a colorless oil, which solidified on standing. Recrystallization from *n*-hexane/$CH_2Cl_2$ gave an analytical sample. Mp: 144−145 °C. IR ($CHCl_3$) $cm^{-1}$: 3482, 1637, 1112. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.09 (s, 3H), 1.26−1.31 (m, 2H), 1.43−1.59 (m, 6H), 1.70 (d, $J$ = 11.0 Hz, 1H), 1.72−1.84 (m, 4H), 1.86−2.01 (m, 2H), 1.92 (s, 3H), 2.09−2.24 (m, 4H), 2.39 (dd, $J$ = 14.0, 8.0 Hz, 1H), 2.54 (dd, $J$ = 14.0, 7.0 Hz, 1H), 3.79−3.99 (m, 4H), 5.12 (dd, $J$ = 17.0, 1.0 Hz, 1H), 5.18 (dd, $J$ = 10.0, 2.5 Hz, 1H), 5.91−6.00 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz): 19.1, 23.2, 24.8, 27.9, 29.5, 30.8, 34.2, 34.7, 35.1, 35.3, 41.0, 41.1, 43.4, 45.8, 46.4, 63.9, 64.6, 76.5, 111.9, 118.9, 132.4, 134.4, 140.5. MS (FAB) *m*/*z*: 359 ($MH^+$, 55), 317 (100). HRMS (FAB): calcd for $C_{23}H_{35}O_3$ ($MH^+$) 359.2586, found 359.2592.

**(±)-(1*S**,2*S**,6*S**,7*S**,10*R**,12*R**)-2-Methyl-8,13-dioxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecane-6-carbonitrile 13,-13-Ethylene Acetal (20).** A solution of the enone **19** (145 mg, 0.48 mmol) in benzene (1.4 mL) was added dropwise to a stirred solution of $Et_2AlCN$ (1.0 M in toluene, 1.4 mL) at 0 °C. After being stirred for 1.5 h at 0 °C, a viscous solution of $Et_3N$ (0.625 mL, 4.50 mmol) and TMSCl (0.295 mL, 2.34 mmol) in benzene (0.4 mL) was added using a cannula. The resulting mixture was warmed to room temperature, and $Et_2O$ (20 mL) and saturated aqueous $NaHCO_3$ (9 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 MeOH−benzene (10:1; 4 mL), and $K_2CO_3$ (130 mg) was added. The mixture was stirred for 10 min at 0 °C, dried ($Na_2SO_4$), filtered, and concentrated. Purification of the residue by column chromatography (1:1 hexane/EtOAc) gave 128 mg (81%) of **20** as a colorless solid. Recrystallization (*n*-hexane/$CH_2Cl_2$) provided analytically pure coarse powder. Mp: 124−126 °C. IR (KBr) $cm^{-1}$: 2227, 1708. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.22 (s, 3H), 1.37−1.46 (m, 3H), 1.59−1.75 (m, 6H), 1.86−1.97 (m, 4H), 2.13−2.15 (m, 1H), 2.26 (t, $J$ = 7.0 Hz, 1H), 2.34 (t, $J$ = 14.5 Hz, 1H), 2.46−2.54 (m, 1H), 2.57 (dd, $J$ = 13.5, 3.5 Hz, 1H), 2.66 (d, $J$ = 3.5 Hz, 1H), 3.10 (br s, 1H), 3.84−4.01 (m, 4H).$^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 15.7, 18.7, 23.8, 25.6, 29.2, 29.8, 29.9, 32.7, 34.0, 39.9, 42.5, 42.8, 43.5, 47.6, 52.7, 64.0, 64.6, 111.2, 122.0, 207.1. MS (EI) *m*/*z*: 329 ($M^+$, 4.3), 99 (100). HRMS (EI): calcd for $C_{20}H_{27}NO_3$ 329.1993, found 329.1991. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.63; H, 8.14; N, 4.10.

**(±)-(1*S**,2*S**,6*S**,7*S**,8*R**,10*R**,12*R**)-8-Hydroxy-2-methyl-13-oxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecane-6-carbonitrile 13,13-Ethylene Acetal (21).** To a solution of the ketone **20** (424 mg, 1.29 mmol) in MeOH−THF (7:5, 12 mL) was added $NaBH_4$ (38 mg, 1.00 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 45 min. Aqueous $NH_4Cl$

(excess) was added. The whole was concentrated, and the concentrate was dissolved in $CH_2Cl_2$, 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 426 mg (100%) of **21** as a colorless foam. Recrystallization from *n*-hexane/$CH_2Cl_2$ provided colorless needles. Mp: 143−146 °C. IR (KBr) $cm^{-1}$: 3471, 2233, 1115. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.26−1.31 (m, 2H), 1.44 (s, 3H), 1.47−1.66 (m, 9H), 1.75−1.85 (m, 4H), 1.89−1.96 (m, 2H), 2.09−2.12 (m, 1H), 2.17 (t, $J$ = 6.0 Hz, 1H), 2.64−2.72 (m, 1H), 2.87 (m, 1H), 3.82−3.99 (m, 4H), 4.02 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 17.0, 19.0, 25.7, 28.9, 29.5, 30.2, 31.4, 33.9, 35.0, 35.1 (2C), 40.5, 43.1, 43.7, 47.4, 63.9, 64.5, 73.0, 111.7, 124.2. MS (FAB) *m*/*z*: 332 ($MH^+$, 12.2), 307 (100). HRMS (FAB): calcd for $C_{20}H_{30}NO_3$ ($MH^+$) 332.2226, found 332.2231.

**(±)-(1*S**,2*S**,6*S**,7*S**,8*R**10*R**,12*R**)-2-Methyl-13-oxo-8-[(trimethylsilyl)oxy]tetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecane-6-carbonitrile 13,13-Ethylene Acetal (22).** To a solution of the alcohol **21** (125 mg, 0.377 mmol) in $CH_2Cl_2$ (1.5 mL) were added DMAP (17 mg, 0.139 mmol) and pyridine (1.18 mL) at 0 °C. Freshly distilled TMSCl (0.28 mL, 2.21 mmol) was then added, and the mixture was stirred at 0 °C for 2 h. Saturated $NaHCO_3$ (10 mL) was added, and the reaction mixture was extracted with $CH_2Cl_2$, dried ($Na_2SO_4$), and concentrated. The concentrate was purified by column chromatography (3:2 hexane/EtOAc) to give **22** (149 mg, 98%) as a crystalline solid. Recrystallization from *n*-hexane provided **22** as a colorless solid. Mp: 166−167 °C. IR (KBr) $cm^{-1}$: 2227, 1114. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 0.17 (s, 9H), 1.20−1.28 (m, 4H), 1.39 (s, 3H), 1.46−1.65 (m, 8H), 1.71−1.80 (m, 2H), 1.85−1.92 (m, 2H), 2.06−2.09 (m, 1H), 2.13−2.18 (m, 1H), 2.60−2.67 (m, 1H), 2.67−2.70 (m, 1H), 3.82−4.00 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 0.09 (3C), 16.7, 19.2, 25.9, 29.50, 29.53, 30.3, 32.1, 33.7, 34.7, 35.0, 35.2, 40.6, 43.1, 44.2, 47.3, 63.9, 64.5, 73.0, 111.8, 123.8. MS (EI) *m*/*z*: 403 ($M^+$, 5.9), 389 (23.3), 316 (100). HRMS (EI): calcd for $C_{23}H_{37}NO_3Si$ ($M^+$) 403.2543, found 403.2541.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**10*R**,12*R**)-6-[(Benzyloxy)methyl]-2-methyl-13-oxo-8-[(trimethylsilyl)oxy]tetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecane-6-carbonitrile 13,13-Ethylene Acetal (23).** To a stirred solution of diisopropylamine (0.085 mL, 0.606 mmol) in THF (0.75 mL) was added *n*-BuLi (1.59 M in hexane; 0.375 mL, 0.596 mmol) dropwise at −78 °C, and the mixture was warmed to 0 °C for 30 min. Then a solution of the nitrile **22** (82 mg, 0.203 mmol) in THF (0.85 mL) was added dropwise, and the resulting solution was stirred for 20 min. The solution obtained was cooled to −78 °C, and freshly distilled benzyloxymethyl chloride (0.108 mL, 0.775 mmol) was added rapidly. The reaction mixture was warmed to 0 °C. After being stirred at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (excess). The whole was then extracted with $CH_2Cl_2$, and the extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the concentrate by flash chromatography (8:1 hexane/EtOAc) yielded 95 mg (89%) of **23** as a colorless oil. IR (KBr) $cm^{-1}$: 2231, 1115. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 0.06 (s, 9H), 1.20−1.27 (m, 2H), 1.41 (s, 3H), 1.42−1.97 (m, 15H), 2.14 (br s, 1H), 2.55−2.62 (m, 1H), 3.39 (d, $J$ = 9.0 Hz, 1H), 3.57 (d, $J$ = 9.0 Hz, 1H), 3.82−4.00 (m, 4H), 4.02 (m, 1H), 4.46 (d, $J$ = 12.0 Hz, 1H), 4.61 (d, $J$ = 12.0 Hz, 1H), 7.30−7.39 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 0.44 (3C), 17.0, 19.4, 25.8, 29.5, 30.3, 33.2, 34.3, 35.0, 35.4, 36.0, 38.7, 40.6, 43.1, 44.1, 47.6, 63.9, 64.5, 68.0, 73.3, 73.5, 111.8, 123.9, 127.8 (2C), 128.0, 128.5 (2C), 137.5. MS (FAB) *m*/*z*: 524 ($MH^+$, 72), 91 (100). HRMS (FAB): calcd for $C_{31}H_{46}NO_4Si$ ($MH^+$) 524.3196, found 524.3218.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**)-6-[(Benzyloxy)methyl]-8-hydroxy-6-hydroxymethyl-2-methyltetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecan-13-one 13,13-Ethylene Acetal (25).** To a solution of the nitrile **23** (21 mg, 0.040 mmol) in THF (1.4 mL) was added $LiAlH_4$ (1.0 M in ether; 0.65 mL) at 0 °C, and the resulting mixture was warmed to room temperature and then refluxed at 75 °C for 4 h. The solution was cooled to 0 °C and quenched by successive addition of $H_2O$ (25 $\mu$L), 2 N NaOH (25 $\mu$L), and $H_2O$ (80 $\mu$L). The resulting heterogeneous mixture was stirred at room temperature for 2 h and filtered, and the solid was washed with EtOAc. The combined filtrate was concentrated to give the amine **24**. The crude amine **24**, KOH (110 mg, 1.93 mmol), and degassed diethylene glycol (0.9 mL) were placed under $N_2$ in a round-bottom flask equipped with a refluxing condenser. The mixture was heated at 210 °C for 4 h. The dark solution was then cooled to room temperature, and $Et_2O$ (3 mL) and $H_2O$ (2 mL) were added. The organic phase was separated, and the aqueous layer was extracted with $Et_2O$ (5 × 6 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatography (5:1 hexane/EtOAc) gave 12 mg (63%, two steps) of the diol **25** as a solid mass. Crystallization from benzene provided a pure white solid. Compound **25**. Mp: >300 °C. IR (KBr) $cm^{-1}$: 3267 (br), 1115. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.16 (d, $J$ = 10.5 Hz, 1H), 1.25−1.29 (m, 4H), 1.31 (s, 3H), 1.39−1.72 (m, 10H), 1.77−1.93 (m, 4H), 2.14 (m, 1H), 2.63−2.70 (m, 1H), 3.41 (d, $J$ = 9.0 Hz, 1H), 3.47 (d, $J$ = 9.0 Hz, 1H), 3.53 (d, $J$ = 12.0 Hz, 1H), 3.82−4.00 (m, 4H), 4.23 (d, $J$ = 2.0 Hz, 1H), 4.32 (d, $J$ = 12.0 Hz, 1H), 4.47 (d, $J$ = 12.5 Hz, 1H), 4.53 (d, $J$ = 12.5 Hz, 1H), 7.28−7.37 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.5, 18.7, 26.4, 29.7, 30.5, 33.5, 34.9, 35.4, 35.8, 35.9, 40.8, 43.0, 43.1, 46.8, 48.5, 63.9, 64.5, 67.6, 67.7, 73.4, 79.0, 111.9, 127.5 (2C), 127.7, 128.5 (2C), 138.2. MS (FAB) *m*/*z*: 457 ($MH^+$, 10.8), 212 (100), 91 (84). HRMS (FAB): calcd for $C_{28}H_{41}O_5$ ($MH^+$) 457.2954, found 457.2954.

**(±)-(1*S**,2*S**,6*S**,7*R**,8*R**,10*R**,12*R**)-6-[(Benzyloxy)methyl]-8-hydroxy-2-methyl-13-oxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecane-6-carboaldehyde 13,13-Ethylene Acetal (26).** $RuCl_2(PPh_3)_3$ (30 mg, 0.031 mmol) was added to a solution of the diol **25** (14 mg, 0.0307 mmol) in benzene (0.7 mL), and the resulting mixture was stirred in the presence of air at room temperature for 24 h. The dark solution obtained was passed through a short silica gel column eluting with EtOAc. The eluate was then concentrated, and the residue was chromatographed on silica gel (3:1 hexane/EtOAc) to afford **26** (10 mg, 72%) as a colorless oil, together with 3.0 mg (21%) of the recovered diol **25**. Compound **26**. IR (KBr) $cm^{-1}$: 3493, 1705, 1115. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.00 (s, 3H), 1.16−1.29 (m, 4H), 1.51−1.69 (m, 8H), 1.76−1.83 (m, 2H), 1.88−1.94 (m, 2H), 2.14 (t, $J$ = 7.0 Hz, 1H), 2.32 (d, $J$ = 13.0 Hz, 1H), 2.57−2.65 (m, 1H), 3.35 (s, 1H), 3.44 (d, $J$ = 8.5 Hz, 1H), 3.55 (d, $J$ = 8.5 Hz, 1H), 3.81−3.99 (m, 4H), 4.28 (br s, 1H), 4.42 (d, $J$ = 12.0 Hz, 1H), 4.47 (d, $J$ = 12.0 Hz, 1H), 7.25−7.36 (m, 5H), 10.19 (s, 1H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.8, 19.0, 26.2, 29.6, 30.4, 32.7, 33.3, 34.7, 34.8, 35.1, 35.7, 40.6, 43.2, 43.5, 48.7, 63.9, 64.5, 67.9, 73.6, 76.3, 111.7, 127.5 (2C), 127.7, 128.4 (2C), 137.6, 211.1. MS (FAB) *m*/*z*: 477 ($MNa^+$, 16), 176 (100). HRMS (FAB): calcd for $C_{28}H_{38}NaO_5$ ($MNa^+$) 477.2617, found 477.2602.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**)-6-[(Benzyloxy)methyl]-2,6-dimethyl-13-oxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadecan-8-ol 13,13-Ethylene Acetal (27).** A mixture of the aldehyde **26** (24 mg, 0.0528 mmol), $K_2CO_3$ (32 mg, 0.232 mmol), and hydrazine monohydrate (0.6 mL) in diethylene glycol (2 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 3 h. The reaction mixture was cooled to room temperature, and $H_2O$ (2 mL) and $Et_2O$ (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 (2:1 hexane/EtOAc) provided 17 mg (72%) of the title compound **27** as a colorless oil. IR (KBr) $cm^{-1}$: 3494, 1113. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.15 (t, $J$ = 14.5 Hz, 1H), 1.21 (s, 3H), 1.25 (s, 3H), 1.42−1.89 (m, 17H), 2.14 (m, 1H), 2.50−2.55 (m, 1H), 3.00 (d, $J$ = 9.0 Hz, 1H), 3.33 (d, $J$ = 9.0 Hz, 1H), 3.82−4.00 (m, 4H), 4.21 (br s, 1H), 4.45 (d, $J$ = 12.5 Hz, 1H), 4.52 (d, $J$ = 12.5 Hz, 1H), 7.28−7.36 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.4, 18.7, 21.2, 26.3, 29.7, 30.7, 33.8, 35.4, 35.7, 36.0, 38.6, 38.9, 40.7, 43.3, 44.7, 48.2, 63.9, 64.5, 69.3, 73.2, 80.8, 112.0, 127.3 (2C), 127.4, 128.3 (2C), 138.8. MS (FAB)

*m/z*: 441 ($MH^+$, 3.0), 73 (100). HRMS (FAB): calcd for $C_{28}H_{41}O_4$ ($MH^+$) 441.3005, found 441.3024.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**)-6-[(Benzyloxy)-methyl]-2,6-dimethyl-13-oxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-8-yl Benzoate 13,13-Ethylene Acetal (28).** Freshly prepared BzOTf (70 $\mu$L, 0.43 mmol) was added very slowly (dropwise addition by a micropipet) at 0 °C to a well-stirred mixture of the alcohol **27** (18 mg, 0.0409 mmol), 2,6-lutidine (104 $\mu$L, 0.89 mmol), and $CH_2Cl_2$ (0.8 mL). After the mixture was stirred at 0 °C for 2.5 h, $Et_2O$ (4 mL) and saturated aqueous $NaHCO_3$ (0.5 mL) were added. The mixture was warmed to rt and extracted with $Et_2O$, and the extract was washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by a column chromatography (13:1 to 1:1 hexane/EtOAc) yielded 8 mg (37%) of the benzoate **28** along with traces of the undesired enolates **29** and **30**, and 8 mg (44%) of the recovered **27**. Compound **28**. Colorless oil. IR (KBr) cm$^{-1}$: 1713, 1603, 1111. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 0.95 (s, 3H), 1.15−1.25 (m, 4H), 1.45 (s, 3H), 1.60−1.93 (m, 12H), 2.12−2.16 (m, 1H), 2.27 (d, $J$ = 2.5 Hz, 1H), 2.46−2.55 (m, 1H), 2.90 (d, $J$ = 9.0 Hz, 1H), 3.38 (d, $J$ = 9.0 Hz, 1H), 3.83−4.00 (m, 4H), 4.47 (d, $J$ = 13.0 Hz, 1H), 4.58 (d, $J$ = 13.0 Hz, 1H), 5.57 (d, $J$ = 2.5 Hz, 1H), 7.28−7.36 (m, 5H), 7.46 (t, $J$ = 7.5 Hz, 2H), 7.56 (t, $J$ = 7.5 Hz, 1H), 8.05 (d, $J$ = 7.5 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 18.7, 20.6, 26.4, 29.7, 30.5, 32.6, 34.9, 35.4, 35.8, 38.3, 38.6, 40.8, 42.18, 42.23, 43.3, 48.1, 63.9, 64.5, 72.3, 73.1, 79.4, 111.9, 127.2 (2C), 127.3, 128.3 (2C), 128.5 (2C), 129.6 (2C), 131.0, 132.8, 139.0, 166.0. MS (FAB) *m/z*: 545 ($MH^+$, 60), 91 (100). HRMS (FAB): calcd for $C_{35}H_{45}O_5$ ($MH^+$) 545.3267, found 545.3282.

For the data of **29** and **30**, see the Supporting Information.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**)-6-[(Benzyloxy)-methyl]-2,6-dimethyl-13-oxotetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-8-yl Benzoate (31).** Freshly distilled BzOTf (10 $\mu$L, 0.0617 mmol) was added to a stirred solution of the alcohol **27** (7.0 mg, 0.0159 mmol) in $CH_2Cl_2$ (0.3 mL) in a microreactor at −78 °C. After the mixture was stirred at −78 °C for 10 min, $Et_2O$ (0.2 mL) and saturated $NaHCO_3$ (few drops) were added, and the mixture was warmed to room temperature. The whole was extracted with EtOAc, and the extract was washed with water and brine, dried ($MgSO_4$), and concentrated. The concentrate was then purified by column chromatography (6:1 hexane/EtOAc) to provide the keto benzoate **31** (3 mg, 35%), together with **32** (1 mg, 19%) and the bis-benzoate **33** (1 mg, 10%) all as colorless oils, and a mixture of unidentified product (3 mg). Compound **31**. Colorless crystalline solid. Mp: 223−224 °C (*n*-hexane/EtOAc). IR (KBr) cm$^{-1}$: 1716 (br), 1601. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 0.96 (s, 3H), 1.19−1.31 (m, 5H), 1.53 (s, 3H), 1.60−1.77 (m, 4H), 1.95−2.11 (m, 5H), 2.21−2.25 (m, 1H), 2.22 (d, $J$ = 2.5 Hz, 1H), 2.47−2.54 (m, 1H), 2.60−2.69 (m, 2H), 2.91 (d, $J$ = 9.5 Hz, 1H), 3.42 (d, $J$ = 9.5 Hz, 1H), 4.48 (d, $J$ = 12.0 Hz, 1H), 4.57 (d, $J$ = 12.0 Hz, 1H), 5.61 (m, 1H), 7.27−7.37 (m, 5H), 7.47 (t, $J$ = 7.5 Hz, 2H), 7.58 (t, $J$ = 7.5 Hz, 1H), 8.05 (d, $J$ = 7.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 18.5, 19.3, 20.7, 24.9, 29.7, 31.5, 32.5, 34.4, 35.9, 36.2, 36.4, 38.2, 38.5, 40.9, 42.1, 49.0, 71.6, 73.1, 79.1, 127.3 (2C), 127.4, 128.3 (2C), 128.5 (2C), 129.6 (2C), 130.9, 132.9, 138.8, 166.0, 214.7. MS (FAB) *m/z*: 501 ($MH^+$, 27), 91 (100). HRMS (FAB): calcd for $C_{33}H_{41}O_4$ ($MH^+$) 501.3005, found 501.3008.

For the data of **32** and **33**, see the Supporting Information.

**Preparation of 31 from 28 or 29.** To a solution of **28** (8 mg, 0.0147 mmol) in acetone (0.5 mL) was added 1 N HCl (10 $\mu$L), and the resulting solution was heated at 40 °C for 30 min. Saturated aqueous $NaHCO_3$ (few drops) was added, and then the organic solvent was evaporated. The aqueous layer was extracted with $CH_2Cl_2$, and the extract was washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue by column chromatography (5:1 hexane/EtOAc) gave **31** (6 mg, 76%) with 1 mg (10%) of the recovered benzoate **28**. Similarly, **29** (4 mg, 0.0058 mmol) was converted to **31** (2 mg) in 66% yield.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**,13*R**)-6-[(Benzyloxy)-methyl]-13-hydroxy-2,6,13-trimethyltetracyclo[10.3.1.0$^{1,10}$.0$^{2,7}$]-hexadec-8-yl Benzoate (34) and Its (±)-(1*S**,2*S**,6*R**,7*R**,8*R**,-10*R**,12*R**,13*S**)-Isomer (35).** MeLi (1.14 M in $Et_2O$; 25 $\mu$L, 0.0285 mmol) was added dropwise at −78 °C to a stirred solution of the ketone **31** (5 mg, 0.0104 mmol) in THF (0.5 mL) in a microreactor, and the resulting mixture was stirred at −78 °C for 10 min. Saturated aqueous $NH_4Cl$ was added at −78 °C, and the reaction mixture was warmed to room temperature. The whole was extracted with $CH_2Cl_2$, and the combined extract was washed with brine, dried ($MgSO_4$), and concentrated. The concentrate was purified by column chromatography (6:1 hexane/EtOAc) to give **34** (2 mg, 43%) and **35** (2 mg, 37%) (combined yield 80%). In another run, when **31** was stirred with a freshly prepared and distilled MeTi(O-*i*-Pr)$_3$ (excess) at room temperature for 18 h, **34** was detected as the single isomer by the TLC and 500 MHz $^1$H NMR spectrum. The yield of **34**, calculated by the $^1$H NMR spectrum was 66%.

Compound **34**. Colorless oil. IR (KBr) cm$^{-1}$: 3487, 1713, 1601. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 0.95 (s, 3H), 0.96 (dd, $J$ = 14.0, 7.0 Hz, 1H), 1.14 (s, 3H), 1.18−1.90 (m, 16H), 1.44 (s, 3H), 2.00 (t, $J$ = 7.3 Hz, 1H), 2.28 (d, $J$ = 3.0 Hz, 1H), 2.42−2.49 (m, 1H), 2.91 (d, $J$ = 9.0 Hz, 1H), 3.39 (d, $J$ = 9.0 Hz, 1H), 4.48 (d, $J$ = 12.0 Hz, 1H), 4.57 (d, $J$ = 12.0 Hz, 1H), 5.57 (d, $J$ = 3.0 Hz, 1H), 7.31−7.36 (m, 5H), 7.45 (t, $J$ = 8.0 Hz, 2H), 7.56 (t, $J$ = 7.0 Hz, 1H), 8.04−8.06 (m, 2H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 18.6, 18.7, 20.7, 25.2, 28.1, 29.7, 31.6, 32.8, 33.3, 34.6, 35.8, 38.4, 38.7, 40.9, 42.1, 46.8, 48.1, 72.4, 72.8, 73.1, 79.5, 127.2 (2C), 127.3, 128.3 (2C), 128.5 (2C), 129.6 (2C), 131.1, 132.8, 139.0, 166.0. MS (FAB) *m/z*: 539 ($MNa^+$, 3.3), 91 (100). HRMS (FAB): calcd for $C_{34}H_{44}NaO_4$ ($MNa^+$) 539.3137, found 539.3156.

Compound **35**. Colorless oil. IR (KBr) cm$^{-1}$: 3450, 1716, 1603. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 0.94 (s, 3H), 1.18−1.73 (m, 15H), 1.29 (s, 3H), 1.44 (s, 3H), 1.81−1.84 (m, 1H), 1.87−1.90 (m, 1H), 1.98 (t, $J$ = 6.0 Hz, 1H), 2.26 (d, $J$ = 2.5 Hz, 1H), 2.44−2.52 (m, 1H), 2.90 (d, $J$ = 9.0 Hz, 1H), 3.39 (d, $J$ = 9.0 Hz, 1H), 4.47 (d, $J$ = 12.5 Hz, 1H), 4.58 (d, $J$ = 12.5 Hz, 1H), 5.57 (d, $J$ = 2.5 Hz, 1H), 7.28−7.36 (m, 5H), 7.46 (t, $J$ = 8.0 Hz, 2H), 7.56 (t, $J$ = 7.5 Hz, 1H), 8.05 (d, $J$ = 7.5 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 18.7, 20.6, 26.6, 26.9, 28.9, 29.7, 32.0, 34.0, 34.7, 35.8, 35.9, 38.3, 38.6, 40.7, 42.2, 47.6, 48.5, 72.3, 72.9, 73.1, 79.4, 127.2 (2C), 127.3, 128.3 (2C), 128.5 (2C), 129.6 (2C), 131.1, 132.8, 139.0, 166.0. MS (FAB) *m/z*: 539 ($MNa^+$, 25), 91 (100). HRMS (FAB): calcd for $C_{34}H_{44}NaO_4$ ($MNa^+$) 539.3137, found 539.3146.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**,13*R**)-13-Hydroxy-6-(hydroxymethyl)-2,6,13-trimethyltetracyclo-[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-8-yl Benzoate (36).** A flask containing the alcohol **34** (6 mg, 0.0107 mmol) and 10% Pd/C (6 mg) was evacuated and then flushed with $H_2$ for several times. Freshly distilled MeOH (0.8 mL) was added, and $H_2$ was bubbled into the stirred mixture for few minutes. The mixture was stirred at room temperature under a $H_2$ atmosphere for 12 h. The reaction mixture was passed through a plug of silica gel eluting with EtOAc, the eluate was concentrated. Purification of the residue by a column chromatography (2:1 hexane/EtOAc) afforded 4 mg (88%) of **36** as a colorless oil. IR (KBr) cm$^{-1}$: 3464, 3446, 1713. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 0.95 (s, 3H), 0.96 (dd, $J$ = 13.5, 8.0 Hz, 1H), 1.14 (s, 3H), 1.16−1.91 (m, 17H), 1.46 (s, 3H), 2.01 (t, $J$ = 7.0 Hz, 1H), 2.16 (d, $J$ = 2.5 Hz, 1H), 2.44−2.50 (m, 1H), 3.11 (d, $J$ = 10.5 Hz, 1H), 3.58 (d, $J$ = 10.5 Hz, 1H), 5.64 (d, $J$ = 2.5 Hz, 1H), 7.47 (t, $J$ = 8.0 Hz, 2H), 7.57 (t, $J$ = 7.0 Hz, 1H), 8.05−8.07 (m, 2H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 18.7 (2C), 20.3, 25.1, 28.1, 29.7, 31.5, 32.8, 33.3, 34.5, 35.8, 38.1, 38.6, 40.9, 41.9, 46.8, 48.1, 71.9, 72.2, 72.8, 128.5 (2C), 129.7 (2C), 131.0, 132.8, 166.1. MS (FAB) *m/z*: 449 ($MNa^+$, 40), 176 (100). HRMS (FAB): calcd for $C_{27}H_{38}NaO_4$ ($MNa^+$) 449.2668, found 449.2667.

**(±)-Scopadulin (4).** $NaIO_4$ (45 mg, 0.21 mmol) was added to a solution of **36** (4.0 mg, 0.0094 mmol) in a mixed solvent of $CCl_4$−$CH_3CN$−$H_2O$ (1:1:1.5; 0.35 mL) in a microreactor, and the mixture was stirred at room temperature for 20 min. $RuCl_3 \cdot 3H_2O$ (about 0.5 mg) was added, and the mixture was stirred overnight at room temperature. After 15 h, the reaction mixture was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was dried ($MgSO_4$),

filtered, and concentrated, and the residue was purified by column chromatography (1:2 hexane/EtOAc to EtOAc to 7:3 EtOAc/MeOH) to give (±)-scopadulin **4** (3 mg, 63%) as a white solid. Recrystallization from EtOAc provided an analytically pure colorless solid. Mp: 238−240 °C. IR (KBr) $cm^{-1}$: 3436 (br), 1716, 1701, 1603. $^1H$ NMR ($C_5D_5N$, 500 MHz) $\delta$: 1.06 (dd, $J$ = 13.0, 8.0 Hz, 1H), 1.27−1.30 (m, 2H), 1.29 (s, 3H), 1.50−1.61 (m, 4H), 1.59 (s, 3H), 1.74 (s, 3H), 1.78−1.89 (m, 7H), 2.11−2.24 (m, 4H), 2.43 (d, $J$ = 11.0 Hz, 1H), 2.62−2.68 (m, 1H), 3.03 (d, $J$ = 2.0 Hz, 1H), 6.03 (d, $J$ = 2.0 Hz, 1H), 7.50−7.57 (m, 3H), 8.34 (d, $J$ = 8.0 Hz, 2H). $^{13}C$ NMR ($C_5D_5N$, 125 MHz) $\delta$: 18.7 19.0, 20.2, 25.7, 28.6, 31.6, 33.2, 33.5, 33.9, 35.3, 36.0, 40.6, 41.1, 44.5, 47.6, 48.1, 48.6, 71.4, 75.2, 129.1 (2C), 130.0 (2C), 131.7, 133.3, 166.2, 182.8. MS (FAB) *m*/*z*: 441 ($MH^+$, 29), 185 (100). HRMS (FAB): calcd for $C_{27}H_{37}O_5$ ($MH^+$) 441.2641, found 441.2631.

**(±)-(1*S**,2*S**,6*R**,7*R**,8*R**,10*R**,12*R**,13*S**)-13-Hydroxy-6-(hydroxymethyl)-2,6,13-trimethyltetracyclo-[10.3.1.0$^{1,10}$.0$^{2,7}$]hexadec-8-yl Benzoate (37).** According to the procedure for the synthesis of **36** from **34**, the benzyl ether **35** (5 mg, 0.0093 mmol) was converted into **37** (3 mg, 76%) as a colorless oil. IR (KBr) $cm^{-1}$: 3410 (br), 1709, 1618. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 0.94 (s, 3H), 1.16−1.28 (m, 4H), 1.30 (s, 3H), 1.41−1.77 (m, 12H), 1.45 (s, 3H), 1.82−1.86 (m, 1H), 1.90 (dt, $J$ = 14.0, 3.0 Hz, 1H), 1.99 (t, $J$ = 6.5 Hz, 1H), 2.14 (d, $J$ = 3.0 Hz, 1H), 2.46−2.53 (m, 1H), 3.10 (d, $J$ = 11.0 Hz, 1H), 3.59 (d, $J$ = 11.0 Hz, 1H), 5.64 (m, 1H), 7.46 (t, $J$ = 7.0 Hz, 2H), 7.57 (t, $J$ = 7.5 Hz, 1H), 8.04−8.06 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$: 18.6, 18.8, 20.3, 26.5, 26.9, 28.9, 32.0, 34.0, 34.7, 35.8, 35.9, 38.0, 38.6, 40.7, 42.0, 47.5, 48.5, 71.8, 72.1, 72.9, 128.5 (2C), 129.6 (2C), 131.0, 132.8, 166.1. MS (FAB) *m*/*z*: 449 ($MNa^+$, 6.0), 176 (100). HRMS (FAB): calcd for $C_{27}H_{38}NaO_4$ ($MNa^+$) 449.2668, found 449.2661.

**16-*epi*-Scopadulin (4a)**: According to the procedure for the synthesis of **4** from **36**, the alcohol **37** (3 mg, 0.0061 mmol) was converted into **38** (1 mg, 43%) as a colorless oil. IR (KBr) $cm^{-1}$: 3421, 3327 (br), 1716 (br), 1603. $^1H$ NMR ($C_5D_5N$, 500 MHz) $\delta$: 1.21−1.97 (m, 16H), 1.50 (s, 3H), 1.58 (s, 3H), 1.74 (s, 3H), 2.09−2.17 (m, 1H), 2.13 (d, $J$ = 13.0 Hz, 1H), 2.24 (t, $J$ = 6.8 Hz, 1H), 2.60−2.66 (m, 1H), 2.96 (br s, 1H), 6.00 (br s, 1H), 7.49−7.55 (m, 3H), 8.33−8.34 (m, 2H). $^{13}C$ NMR ($C_5D_5N$, 125 MHz) $\delta$: 18.8 19.0, 22.0, 27.0, 27.6, 30.0, 32.5, 33.5, 34.8, 35.2, 35.9, 40.6, 40.9, 42.8, 44.6, 48.2, 49.1, 71.6, 75.1, 129.1 (2C), 130.0 (2C), 131.7, 133.3, 164.8, 179.6. MS (FAB) *m*/*z*: 463 ($MNa^+$, 3.2), 176 (100). HRMS (FAB): calcd for $C_{27}H_{36}NaO_5$ ($MNa^+$) 463.2460, found 463.2459.

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**Supporting Information Available:** Augmented and updated data of compound **19** and the intermediates for the synthesis of **19** from **9**; characterization of **29**, **30**, **32**, and **33**; $^1H$ and $^{13}C$ NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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