A New Synthetic Approach to Forskolin: Construction of the ABC Ring System from D-Galactose

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Intramolecular Diels−Alder reaction of dienyne **14** afforded naphthopyran **18** which underwent 1,4-addition of methyl copper reagent to give the functionalized tricyclic system of forskolin **17**. The synthesis of dienyne **14** is based on a stereoselective introduction of carbon side chains at C(1) and C(2) of tri-*O*-acetyl-D-galactal via C-Ferrier followed by Claisen−Ireland rearrangements.

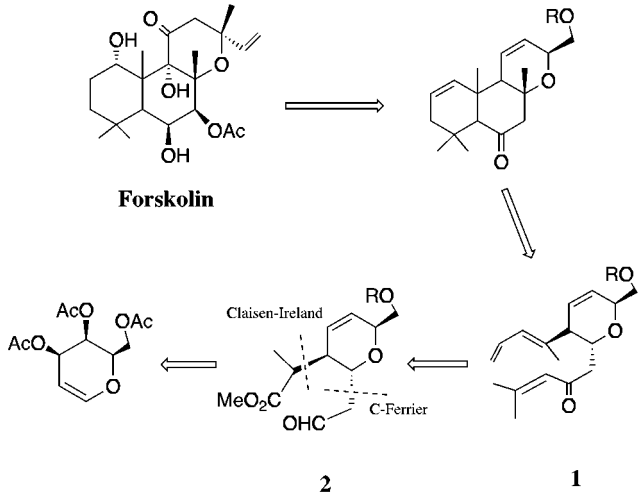
Forskolin, a highly oxygenated labdane diterpene, exhibits a broad range of physiological activities through its ability to activate adenylate cyclase. The therapeutic potential of this natural product combined with its highly challenging structure has served to stimulate an important synthetic activity in a number of laboratories.[1,2]

In the majority of previous synthetic approaches, an intramolecular Diels−Alder reaction was selected as the key step for the construction of an adequately functionalized AB ring system. In almost all cases, the elaboration of ring C was carried out in the final stages of the synthesis. In a new synthetic approach, we envisioned the construction of the ABC ring system of forskolin starting from the C ring by using a suitably functionalized tetrahydropyran subunit. An added feature of our design lies in the use of the "chiron approach",[3] where the intermediates could be constructed from optically active starting materials. The presence of the tetrahydropyran C ring obviously suggested the choice of carbohydrate derivatives as chiral building blocks. The sugar therefore serves as more than a source of chirality: the ring will form an integral part of the structure of the target.

Carbohydrates have been extensively exploited in the synthesis of carbocyclic natural products.[4] In particular, a whole series of synthetic routes have been described in which conjugated enal and dienes derived from carbohydrates were used in Diels−Alder reactions to obtain chiral carbocyclic systems as intermediates in the synthesis of natural products.[5]

Our strategy, outlined in Scheme 1, involves an intramolecular Diels−Alder cyclization of trienone **1** which should simultaneously assemble the A and B rings of the tricyclic skeleton of forskolin. The success of such an approach depends on two crucial requirements: (a) the regio- and stereocontrolled introduction of substituents at C(1) and C(2) into the sugar, and (b) the degree to which trienones such as **1** undergo Diels−Alder cyclization.

Scheme 1



Examination of the structure of **1** reveals the presence of two vicinal functionalized chains: the dienophile and the diene moities with (1*R*) (2*R*) trans orientation. The need for carbon branches at C(1) and C(2) with the correct sense of chirality suggested the use of galactal derivative **2**, which is readily available from D-galactose, as the starting material. We believed that these substituents could be introduced successively by way of Ferrier and Claisen−Ireland rearrangements. We describe here the preparation of trienones **1** by stereoselective addition of carbon branches at C(1) and C(2) of D-galactal and their reactivity under Diels−Alder reaction conditions.[6]

The synthesis (Scheme 2) was initiated by introduction of the allyl group at C(2) using the carbon-Ferrier

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.

(1) For total syntheses of forskolin see: (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115−8116. (b) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670−3672. (c) Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672−3673. (c) Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1015−1018 and 1019−1022. Calvo, D.; Port, M.; Delpech, B.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1023−1024 .

(2) For an exhaustive review on synthetic routes to forskolin see: Colombo, M. I.; Zinezuk, J.; Ruveda, E. A. *Tetrahedron* **1992**, *48*, 963−1037. For recent syntheses of the "Ziegler intermediate" see: Leclaire, M.; Pericaud, F.; Lallemand, J.-Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1333−1334. Anies, C.; Pancrazi, A.; Lallemand, J.-Y.; Prangé, T. *Bull. Soc. Chim. Fr.* **1997**, *134*, 203−222.

(3) (a) Fraser-Reid, B.; Anderson, R. C. *Fortsch. Chem. Org. Naturst.* **1980**, 39. (b) Hanessian, S. *Total Synthesis of Natural Products: the Chiron Approach*; Pergamon: Oxford, **1983**.

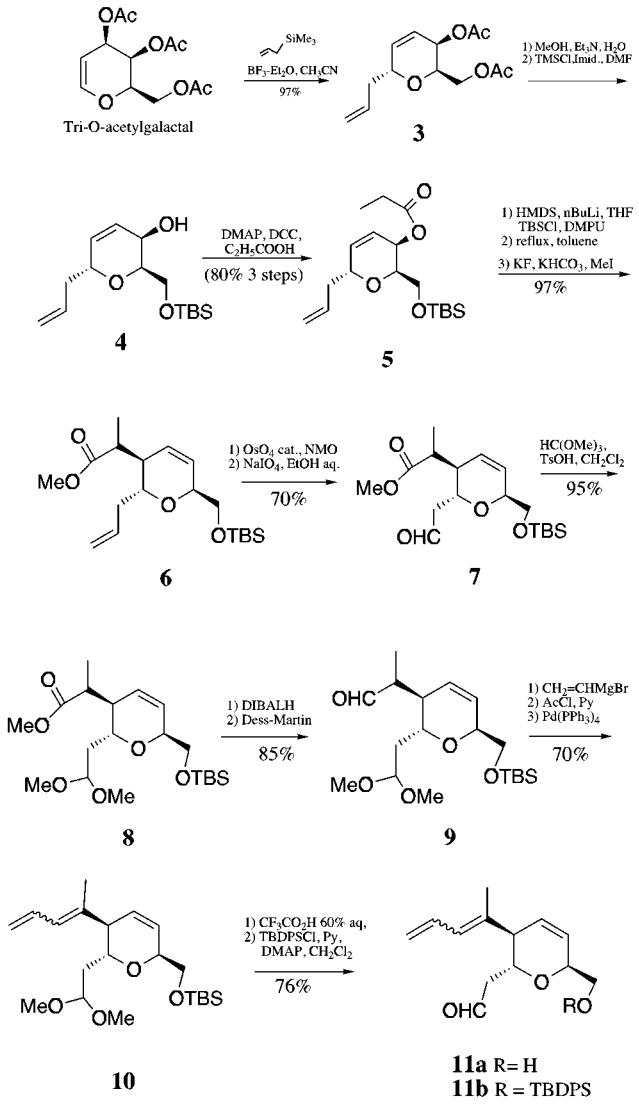
(4) For a recent review see: Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2776−2831. Fraser-Reid, B.; Tsang, R. In *Strategy and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, pp 123−162.

(5) For recent examples see: (a) Lopez, J. C.; Lameignière, E.; Burnouf, C.; Laborde, A. A.; Ghini, A. A.; Olesker, A.; Lukacs, G. *Tetrahedron* **1993**, *49*, 7701−7722. (b) Lopez, J. C.; Gomez, A. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1993**, 762−764. (c) Herscovici, J.; Delatre, S.; Boumaïza, L.; Antonakis, K. *J. Org. Chem.* **1993**, *58*, 3928−3937. (d) Giuliano, R. M.; Jordan, A. D., Jr.; Gauthier, A. D.; Hoogsteen, K. *J. Org. Chem.* **1993**, *58*, 4979−4988. (e) Tsang, R. B.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065−1067. (f) Bonnert, B. V.; Davies, M. J.; Howarth, J.; Jenkins, P. R.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 27−29. (g) Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *65*, 2947−2949.

(6) Portions of this work have been reported in preliminary form: Hanna, I.; Lallemand, J.-Y.; Wlodyka, P. *Tetrahedron Lett.* **1994**, *35*, 6685−6688.

S0022-3263(97)00999-7 CCC: $14.00

Scheme 2



rearrangement.[7] Thus, treatment of galactal triacetate[8] with allyltrimethylsilane in the presence of BF_3-Et_2O at −50°C cleanly afforded **3** as the single α isomer in 97% yield. Hydrolysis of the acetates with Et_3N in aqueous MeOH followed by protection of the primary hydroxyl group led to allylic alcohol **4**, which upon esterification furnished **5** in good overall yield. At this stage, the carbon chain extension with transfer of asymmetry at C(2) was achieved by Ireland's enolate-Claisen rearrangement.[9] To this end, allyl propionate **5** was treated with LHMDS−THF−DMPU followed by TBDMS(Cl) to give the ketene silyl acetal[10] which was heated in refluxing toluene.[11] The crude rearrangement product was subjected to desilylation and methylation affording **6** as a mixture of methyl epimers (7:1 ratio, ^{1}H NMR)[12] in 97% overall yield after flash chromatography.

Chemoselective cleavage of the terminal double bond in compound **6** was achieved by hydroxylation (cat. OsO_4, NMO)[13] followed by diol cleavage with $NaIO_4$ to give **7** in 70% overall yield. After protection of the aldehyde as a dimethyl acetal ($HC(OMe)_3$, cat. TsOH, CH_2Cl_2, 95%), ester **8** was converted into aldehyde **9** by reduction (excess DIBALH) followed by oxidation of the resulting alcohol (Dess-Martin's periodinane[14]) in 80% yield. Attempts to achieve this transformation in 1 one step using 1 equiv of DIBALH led to a mixture of **9** and the primary alcohol, along with the starting ester.

Elaboration of the diene part at C(2) involved addition of vinylmagnesium bromide to aldehyde **9** followed by dehydration of the resulting mixture of stereoisomeric alcohols. While the Grignard reaction was smoothly effected in THF at −70°C (89%), the elimination proved troublesome. Initial attempts using various dehydrating agents were rather disappointing. The best yields of **10** were obtained with $POCl_3$-Py at 0°C (36%) and with MsCl-Et_3N followed by treatment of the resulting mesylate with diisopropylethylamine and DMPU at 185°C[15] (40%). Fortunately, we found that treatment of the corresponding allylic acetate with $Pd(PPh_3)_4$ in refluxing THF[16], afforded the conjugated diene **10** as a mixture of *E* and *Z* isomers (2:1 ratio, ^{1}H NMR)) in 80% overall yield.

In order to introduce the dienophile moiety, the formyl group was first deprotected. Treatment of **10** with aqueous CF_3COOH in THF at room temperature furnished hydroxy aldehyde **11a**. The primary alcohol was then reprotected as its *tert*-butyldiphenylsilyl ether **11b**. All attempts to hydrolyze selectively the dimethyl acetal group in the presence of the *tert*-butyldimethylsilyl ether under milder conditions (PPTS, PTSA, aqueous oxalic acid...) led only to the desilylated product, and the formyl protective group was unaffected.

To test the feasibility of the intramolecular Diels−Alder (IMDA) reaction, trienone **12** was prepared by addition of vinylmagnesium chloride to **11b** at −78 °C in THF, giving rise to a mixture of diastereomeric alcohols (85%). These were readily oxidized with Dess−Martin's periodinane reagent[14] leading to the Diels−Alder precursor **12** in 60% overall yield (Scheme 3).

The IMDA reaction of **12** was performed in a sealed tube at 160 °C as a 6.5×10^{-2} M solution in toluene in the presence of few crystals of hydroquinone for 20 h. In contrast to similar carbocyclic systems which gave a single isomer,[18] we found that IMDA reaction of **12**

(7) (a) Danishefsky, S. J.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803−3805. (b) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082−2089.

(8) Although this starting material is commercially available, its price is rather exorbitant. We therefore prepared it according to the published procedure: Kozikowski, A. P.; Jaemoon, L. *J. Org. Chem.* **1990**, *55*, 863−870.

(9) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854−860 and references cited therein.

(10) Under these conditions, the *Z*-ketene silyl acetal is the major product. For a review on regio- and stereoselective formation of enolates see: Heathcock, C. H. In *Modern Synthtic Methods*; Scheffold, R. , Ed.; VCH: Basel, 1992, vol. 6, chapter 1.

(11) It is worthy of note that first attempts to effect this rearrangement in refluxing benzene gave mostly the starting ester. For a study on the stereoelectronic effect on the Claisen rearrangement of carbohydrate glycal ketene acetals see: Curran, D. P.; Suh, Y.-G. *Carbohyr. Res.* **1987**, *117*, 161−191.

(12) The next steps were performed on this mixture, the asymmetry at this center being destroyed later in the synthesis.

(13) For a review see: Schröder, M. *Chem. Rev.* **1980**, *80*, 187−213.

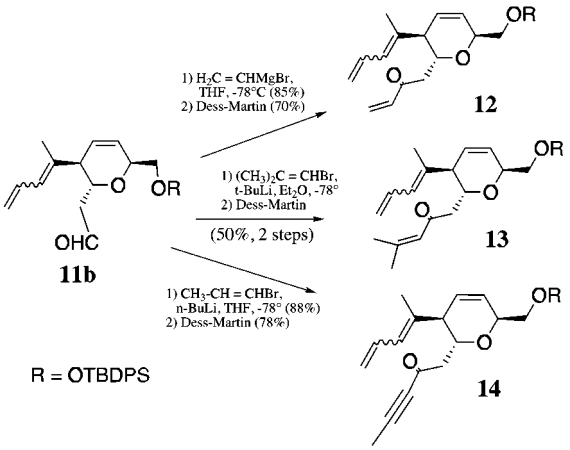
(14) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(15) Kitahara, T.; Matsuoka, T.; Kiyota, H.; Warita, Y.; Kurata, H.; Horiguchi, A.; Mori, K. *Synthsis* **1994**, 692−694.

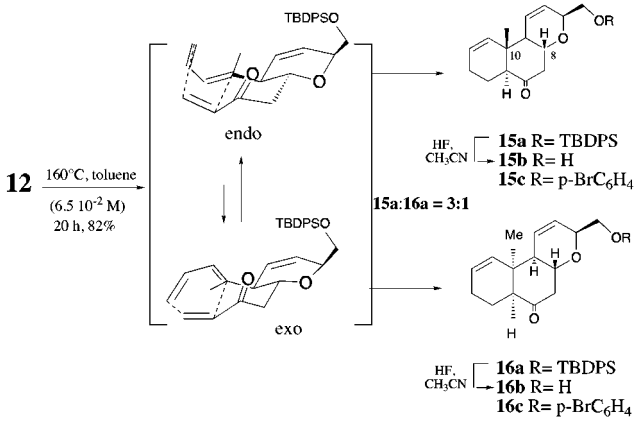
(16) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 301−2304. Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075−2078. For a proposed mechanism see: Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151−11152.

(17) For general reviews on the IMDA reactions see: (a) Roush, W. R. In *Comprhensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 5, pp 513−550. (b) Cigank, E. *Org. React.* **1984**, *32*, 1. (c) Craig, D., *Chem. Soc. Rev.* **1987**, *16*, 187.

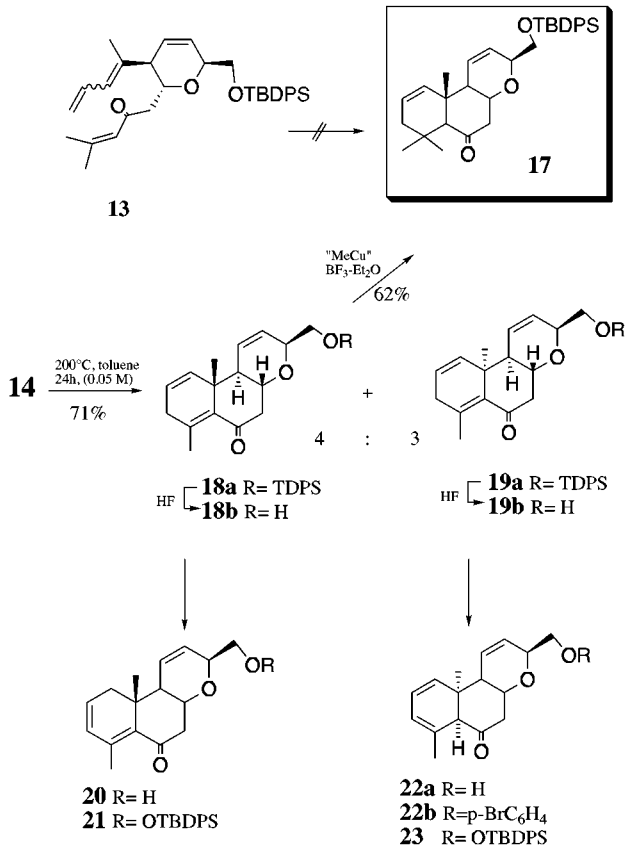
Scheme 3



Scheme 4



Scheme 5



provided a 3:1 mixture of two cycloadducts **15a** and **16a**, separated by flash chromatography in 62 and 20% yield, respectively (Scheme 4). The trans-fused stereochemistry of the major isomer **15a** was deduced by a combination of COSY and NOESY ^{1}H spectra at 400 MHz. In particular, the NOESY experiment revealed a cis relationship of the angular methyl group at C(10) with H(8) (terpenoid numbering). This product may result from a "down side" facial approach of the dienophile which is dictated by the geometrical restriction in the IMDA transition state (Scheme 4). Upon treatment with HF in acetonitrile, **15a** underwent desilylation affording alcohol **15b** having the same AB trans-fused stereochemistry as for **15a**. This compound remained unchanged when subjected either to acidic (BF_3-Et_2O) or basic (NaOMe, MeOH, rt) isomerization conditions.

The stereochemistry of cis-fused product **16a**, the minor component of the mixture, was deduced from the corresponding alcohol **16b** on the basis of NMR spectral data. Of special significance was the strong NOE effect observed between Me(10α) at δ 1.32 ppm and the H(11) vinylic hydrogen at δ 6.17 ppm and the absence of any NOE effect between the angular methyl group and H(8β).

It remained to determine whether trienone **13** could undergo the IMDA cyclization, bearing in mind that the presence of the *gem*-dimethyl group on the dienophile substructure would slow down the rate of cycloaddition.[19] The addition to **11b** of (2-methylpropenyl)lithium, generated from *t*-BuLi and 1-bromo-2-methylpropene, and subsequent oxidation with the Dess−Martin reagent provided trienone **13**. Attempts to accomplish the cycloaddition under both thermal and Lewis acid catalyzed conditions failed to give the desired product **17** (Scheme 5). Thus, when **13** was heated at 180 °C for three days, the starting material was recovered unchanged. In the same manner, treatment of **13** with BF_3-Et_2O in CH_2Cl_2 was also ineffective, and the starting trienone was again unaltered. The greater steric demands imparted by the *gem*-dimethyl group on the transition state are sufficient to impede the cyclization.

In order to overcome this difficulty, the construction of the framework of forskolin was envisaged from tricyclic ketone **18a**, which could be formed *via* the IMDA reaction of dienynone **14**. 1,4-addition of methyl copper reagent to **18a** should then lead to **17** (Scheme 5). To this end, addition to **11b** of 1-propynyllithium, generated by treatment of 1-bromopropene with 2 equiv of *n*-butyllithium at −78 °C,[20] gave rise to a mixture of isomeric alcohols (82%) which were oxidized by Dess−Martin's reagent affording dienynone **14** in 68% overall yield.

Heating a 0.05 M solution of **14** in toluene at 200 °C for 24 h provided a 4:3 mixture of cycloadducts **18a** and

(18) For recent examples of related IMDA cyclization see: Zoller, T.; Uguen, D.; DeCian, A.; Fischer, J.; Sablé, S. *Tetrahedron Lett.* **1997**, *38*, 3409−3412. Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2285−2287. Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 2187−2194.

(19) For recent examples of the IMDA cyclization with a *gem*-dimethyl on the diene see: (a) Bonnert, R. V.; Jenkins, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 413−418. (b) Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 7215−7223. (c) alaima, C. A.; Coburn, C. A.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 6603−6606, and references therein. (d) Gwaltney, S. L. II; Sakata, S. T.; Shea, K. J. *Tetrahedron Lett.* **1995**, *36*, 7177−7180 and references therein. (e) Winkler, J. D.; Kim, H. S.; Kim, S. Ando, K.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 2957−2962.

(20) Suffert, J.; Toussaint; D. *J. Org. Chem.* **1995**, *60*, 3550−3553.

19a, which were separated by flash chromatography in 71% combined yield. Desilylation of these products with HF in acetonitrile at room temperature cleanly gave alcohols **18b** and **19b** in good yield. It is worthy of note that initial attempts to accomplish this reaction using tetrabutylammonium fluoride proved to be troublesome. Thus, treatment of **18a** with TBAF in THF at room temperature resulted in concomitant cleavage of the silyl group as well as the migration of the C(1) double bond leading to conjugated diene **21**. Under the same conditions, cycloadduct **19a** gave **22a** by migration of the C(4) double bond. In this reaction, the fluoride ion obviously acted as a desilylating agent as well as a base. In fact, exposure of both **18a** and **19a** to DBU in refluxing THF for 1 h led to conjugated dienes **20** and **23**, respectively in good yield.

The structure of cycloadducts **18a** and **19a** and their derivatives was established on the basis of ^{1}H NMR, ^{13}C NMR, IR, and mass spectra. The syn relationship between the methyl group at C(10) and (8β) proton in compoud **18b** was deduced from the 2D NOESY spectra which indicated clearly a cross peak between Me(10β) at δ 0.89 ppm and H(8β) at δ 3.88. In contrast, examination of the 2D NOESY spectra of the minor isomer **19b** reveals a strong NOE interaction between the angular methyl at δ 1.07 and H(9α) at δ 3.78, but not with H(8β), which clearly indicated the α-configuration for the methyl group at C(10). The stereochemistry of this carbon was confirmed unambiguously by X-ray analysis of the *p*-bromobenzoate **22b**.[21]

According to the foregoing results, the IMDA cyclization of **14** presumably proceeded through chairlike transition state, with slight preference for the endo orientation. Attempts to improve the selectivity of this reaction by using Lewis acid catalysts were unsuccessful. No reaction occurred when **14** was treated with BF_3-Et_2O, $EtAlCl_2$, or BCl_3 in CH_2Cl_2 at −78 to −50 °C. At higher temperatures, the reaction gave rise to a intractable mixture of products.

Having cycloadduct **18a** in hand, with the right configuration of the angular methyl group at C(10), we next introduced the *gem*-methyl group. Thus, treatment of **18a** with $MeCu\cdot BF_3$ in ether, according to Yamamoto's procedure,[22] provided **17** in 62% yield. The structure of this compound was fully assigned on the basis of its spectroscopic data (See Experimetal Section).

In conclusion, a new route to functionalized tricyclic framework of forskolin has been developed using an intramolecular Diels−Alder reaction for simultaneous construction of A and B rings as the key step. The synthesis of precursor dienyne **14** is based on stereoselective introduction of carbon chains at C(1) and C(2) of tri-*O*-acetyl-D-galactal *via* C-Ferrier followed by Claisen−Ireland rearrangements. The functionalities present in this skeleton provide a handle for further transformations which could lead to forskolin.

Experimental Section

Melting points were determined on a Reichert hot stage apparatus. Infrared spectra were recorded as solutions in CCl_4. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 400 MHz (^{1}H), and at 100.6 or 50.3 MHz (^{13}C) as solutions in $CDCl_3$, using residual protic solvent $CHCl_3$ (δ_H = 7.27) or $CDCl_3$ (δ_C = 77.1) as internal reference. All reactions were monitored by TLC carried out on 0.2 mm Merck aluminum silica gel (60 F_{254}) precoated plates using UV light and 5% ethanolic phosphomolybdic acid and heat as developing agent. Flash chromatography was performed on 40−63 μm (400−230 mesh) silica gel 60 with ethyl acetate−petroleum ether (bp 40−60 °C) (AcOEt−PE) as eluent. Commercially available reagents and solvents were purified and dried when necessary by usual methods.

2(*R*)-(2-Propenyl)-5(*R*)-propanoyloxy-6(*R*)-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,6-dihydro-2*H* pyran (5). To a stirred solution of **4** (13 g, 45.7 mmol) in CH_2Cl_2 (110 mL) cooled to 0 °C was added DMAP (75 mg, 0.61 mmol), and propionic acid (10.3 mL, 139 mmol). Dicyclohexylcarbodiimide DCC (29.2 mL, 139 mmol) in CH_2Cl_2 (40 mL) was then added dropwise, and the resultant mixture was allowed to warm to room temperature. After stirring at this temperature for 5 h 30 min, the mixture was diluted with CH_2Cl_2, and filtered through a pad of Celite. The filtrate was washed with cooled 0.5 N HCl and saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent left a residue which was purified by flash chromatography (AcOEt/EP 5:95 followed by 1/9) to give 15.23 g (98 %) of **5** as colorless oil. R_f 0.42 (AcOEt/PE 1/9); IR 3079, 1736 cm^{-1}; ^{1}H NMR (200 MHz) δ 6.00−6.08 (m, 1H), 5.70−5.87 (m, 1H), 5.01−518 (m, 2H), 4.27 (t, J = 14, 1H), 3.89 (td, J = 6.7, 2.3, 1H), 3.67-3.63 (m, 2H), 2.43−2.24 (m, 4H), 1.08 (t, J = 15.1, 3H), 0.82 (s, 9H), 0.002 (s, 3H), -0.01(s, 3H); ^{13}C NMR (50.3 MHz) δ 173.8 (C), 134.7 (CH), 134.2 (CH), 122.5 (CH), 117.3 (CH_2), 72.6 (CH), 70.6 (CH), 63.5 (CH_2), 61.8 (CH), 36.8 (CH_2), 27.5 (CH_2), 25.7 (3 CH_3), 18.1(C), 9.0 (CH_3), -5.3 (2 CH_3). MS (CI, NH3) m/z (%): 358(0.5) $(M + NH_4)^+$, 341(15), 268(21), 267(100). $[\alpha]_D$ −249° (c 3.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 64.49; H, 9.47. Found C, 64.75; H, 9.41.

Methyl 3(*R*)-[[[2(*R*)-(2-propenyl)-6(*R*)−[[(*tert*-butyldimethylsilyl)oxy] methyl]- 2,3-dihydro-6*H*-pyranyl]propanote (6). Hexamethyldisilazane (HMDS) (5.9 mL, 28.9 mmol) in 75 mL of THF was cooled to −78 °C, and *n*-BuLi (9.8 mL of a 2.5 M solution in hexanes, 24.48 mmol) was added dropwise. After the mixture was stirred for 10 min, TBSCl (4.36 g, 24.48 mmol) dissolved in 20.5 mL of dimethyl tetrahydro-2(1*H*)-pyrimidinone (DMPU) was added, and the reaction solution was stirred for 3 min. Ester **4** (4.68 g, 13.76 mmol) dissolved in 32 mL of THF was then added dropwise, and the mixture was allowed to warm to 0 °C. After stirring at this temperature for 2 h 30 min, the mixture was poured into 270 mL of petroleum ether and washed with 130 mL of ice−water and cold brine and dried ($MgSO_4$) and the solvent removed under reduced pressure.

The residue was briefly dried under high vacuum, and 34 mL of toluene was added. After this solution was refluxed for 7 h, the solvent was again removed, and 17 mL of DMPU was added. Potassium fluoride dihydrate (3.2 g, 41.3 mmol), water (0.5 mL), and potassium bicarbonate (5.5 g, 55 mmol) were added. After 5 min of stirring this suspension at room temperature, methyl iodide (5.5 mL, 68.75 mmol) was added, and the reaction was stirred overnight at ambiant temperature. The product was then extracted with ether, and the organic layer washed with water and brine and dried. The solvent was removed on a rotary evaporator, and the residue was flash chromatographed (AcOEt/EP 93/7) to give 4.7 g of **5** (97%) as a colorless oil of 1:7 inseparable mixture of methyl epimers. Analysis and spectral data of the major isomer: IR 3079, 1737 cm^{-1}. ^{1}H NMR (200 MHz) δ 5.85−5.68 (m, 3H), 5.05 (d, J = 18.9, 1H), 5.01 (d, J = 10 Hz, 1H), 4.02 (m, 1H), 3.86 (t, J = 14, 1H), 3.61 (dd, J = 10, 5.8, 1H), 3.59 (s, 3H), 3.45 (dd, J = 10, 6.3, 1H), 2.55 (t, J = 6.9, 1H), 2.39 (m, 1H), 2.19 (m, 1H), 2.11 (m, 1H), 1.13 (d, J = 7.2, 3H), 0.84 (s, 9H!, 0.005 (s, 6H); ^{13}C NMR (50.3 MHz) δ 175.6 (C), 135.0 (CH), 128.7 (CH), 122.5 (CH), 116.8 (CH_2), 71.8(CH), 69.9 (CH), 65.8 (CH_2), 51.3 (CH_3), 42.5 (CH), 40.3 (CH), 36.8 (CH_2), 25.9 (3 CH_3), 18.3 (C), 14.5 (CH_3), -5.3 (2 CH_3); MS (CI, NH_3) m/z (%): 372(26) $(M + NH_4)^+$, 355(100). Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.66. Found C, 64.44; H, 9.58.

(21) The author has deposited atomic coordinates for **22b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(22) For reviews see: Yamamoto, Y.; Muruyama, K. *J. Am. Chem. Soc.* **1977**, *99*, 947−1038. Yamamoto, Y.; Ibuka, T. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 143−158.

Methyl 2(*R*)-[[[1(*R*)-(2-oxoethyl)-5(*R*)−[[(*tert*-butyldimethylsilyl)oxy]methyl]- 1,2-dihydro-5*H*-pyranyl]]propanote (7). To a stirred solution of the alkene **6** (2 g, 5.634 mmol) in THF (8.4 mL) was added a solution of *N*-methylmorpholine *N*-oxide (NMO) (798 mg, 6.28 mmol) in water (2.8 mL), followed by 0.04 M solution of osmium tetraoxide in *tert*-butyl alcohol (7 mL, 0.28 mmol). After 3 h, a saturated aqueous solution of sodium dithionite ($Na_2S_2O_4$) (30 mL) was added. The mixture was stirred for a further 3 h and then filtered on a pad of Celite, and the filter cake was washed thoroughly with CH_2Cl_2. The solvent was evaporated off under reduced pressure and the resultant oil dissolved in ethanol (51 mL). Aqueous saturated $NaIO_4$ (11.3 mL) was then added to the vigorously stirred solution, followed, after 30 min, by saturated aqueous Na_2SO_3 (14 mL), and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography (AcOEt/EP 1/6, then 1/3) affording 1.4 g (70%) of a 1:7 mixture of epimers **7** as colorless oil. Analysis and spectral data of the major isomer: IR 1731, 1690 cm^{-1}; ^1H NMR (200 MHz) δ 9.8 (s, 1H), 5.89 (dt, J = 10.6, 1.5, 1H), 5.77 (ddd, J = 10.6, 4.4, 1.6, 1H), 4.50 (ddd, J = 8, 5.3, 2.7, 1H), 4.05 (m, 1H), 3.68 (dd, J = 10.0, 3.0, 1H), 3.67 (s, 3H), 3.51 (dd, J = 10, 6.0, 1H), 2.76 (ddd, J = 16.0, 7.9, 3.0, 1H), 2.64 (m, 1H), 2.61 (ddd, J = 16.0, 5.4, 1.5, 1H), 2.20 (m, 1H), 1.24 (d, J = 7.2, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (50.3 MHz) δ 200.7 (C), 176.0 (CH), 128.7 (CH), 125.6 (CH), 70.1 (CH), 67.8 (CH), 65.6 (CH_2), 51.7 (CH_3), 46.6 (CH_2), 42.2 (CH), 40.9 (CH), 26.0 (3 CH_3), 19.1 (C), 14.0(CH_3), -5.4 (2 CH_3); MS (CI, NH_3) m/z (%) : 374(100) $(M + NH_4)^+$, 357(67). Anal. Calcd for $C_{18}H_{32}O_5Si$: C, 60.64; H, 9.03. Found C, 60.75; H, 8.97.

Methyl 3(*R*)-[[[2(*R*)-(2,2-Dimethoxyethyl)-6(*R*)−[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-dihydro-6*H*pyranyl]]propanoate (8). A mixture of **7** (11.2 g, 31.4 mmol), trimethyl orthoformate (25.3 mL, 220 mmol), and *p*-toluenesulfonic acid (150 mg, 0.58 mmol) in CH_2Cl_2 was stirred at room temperature under nitrogen for 30 h. Solid $NaHCO_3$ (1 g, 11.9 mmol) was added, and the solvent was evaporated off under reduced pressure. The resultant residue was flash chromatographed (AcOEt/EP 1/6) to furnish 12.37 g (98%) of **8** as a mixture of epimers. Analysis and spectral data of the major isomer: IR 1737 cm^{-1}; ^1H NMR (200 MHz) δ 5.83 (d, J = 10.5, 1H), 5.73 (dd, J = 10.5, 3.7, 1H), 4.55,(dd, J = 7.6, 3.7, 1H), 4.1 (m, 1H), 3.98 (m, 1H), 3.67 (dd, J = 9.7, 6, 1H), 3.64 (s, 3H), 3.5 (dd, J = 9.7, 6.1, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 2.59 (t, J = 7, 1H), 2.1 (m, 1H), 1.97 (ddd, J = 14.2, 9.3, 3.7, 1H), 1.72 (ddd, J = 14.2, 7.4, 4.6, 1H), 1.2 (d, J = 7.0, 3H), 0.98 (s, 9H), −0.05 (s, 6H); ^{13}C NMR (50.3 MHz) δ 175.4 (C), 128.1 (CH),125.5 (CH), 70.5 (CH), 68.6 (CH), 65.6 (CH_2), 53.0 (CH_3), 52.4 (CH_3), 51.7 (CH_3), 42.3 (CH), 41.1 (CH), 35.3 (CH_2), 25.7 (3 CH_3), 18.2 (C), 14.4 (CH_3), -5.5 (2 CH_3); MS (CI, NH_3) m/z (%): 371(86), 356(35), 313(39), 239(100), 167(53), 75(45).

2(*R*)-(2,2-Dimethoxyethyl)-3(*R*)-(1-methyl-2-oxoethyl)-6(*R*)[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-dihydro-6*H* pyran (9). To a solution of the ester **8** (15.9 g, 39.5 mmol) in ether (280 mL) cooled to −78 °C with stirring was added dropwise a 1.2 M solution of DIBALH in toluene (100 mL, 120 mmol). After being stirred for 20 min at −78 °C, methanol (10 mL) was added and the dry ice bath was removed. More ether (500 mL) was added followed by 480 mL of 5% aqueous sodium potassium tartrate. This biphasic mixture was vigorously stirred for 1 h at room temperature and then separated. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$. The solvent was removed with a rotary evaporator to give 15.1 g of alcohol which was used for the next reaction without further purification.

To a stirred solution of the above alcohol in CH_2Cl_2 (280 mL) was added 0.6 mL of water followed by dess Martin periodinane (DMP) (10.6 g, 25 mmol). After 10 min a second portion of DMP (10.6 g, 25 mmol) was added, and stirring was continued for further 20 min. Ether was added, and the reaction mixture was treated with 1:1 saturated $NaHCO_3$−$Na_2S_2O_3$ solution for 15 min. The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the resultant residue was purified by flash chromatography (AcOEt/EP 1/6, 1/4 and 1/2) to furnish 11.7 g (80% overall) as a colorless oil. Analysis and spectral data of the major isomer: R_f 0.6 (AcOEt/EP 1/4); IR 1727 cm^{-1}; ^1H NMR (200 MHz) δ 9.71 (d, J = 5.4, 1H), 5.87−5.78 (m, 2H), 4.53 (dd, J = 7.9, 3.4, 1H), 4.04 (m, 1H), 3.93 (m, 1H), 3.55 (m, 2H), 3.32 (s, 1H), 3.27 (s, 1H), 2.52 (m, 1H), 2.19 (m, 1H), 1.95 (ddd, J = 12.7, 9.1, 3.4, 1H), 1.75 (ddd, J = 12.7, 7.8, 4.6, 1H), 1.20 (d, J = 7.0, 3H), 1.85 (s, 9H), 0.014 (s, 6H); ^{13}C NMR (50.3 MHz) δ 204.0 (CH), 128.5 (CH), 125.6 (CH), 102.2 (CH), 70.5(CH), 69.6 (CH), 65.6 (CH_2), 52.6 (CH_3), 49.7 (CH_3), 40.1 (CH), 38.7 (CH), 35.5 (CH_2), 25.9 (3 CH_3), 18.4 (C), 11.3(CH_3), −5.3 (2 CH_3); Anal. Calcd for $C_{19}H_{36}O_5Si$: C, 60.95; H, 10.14. Found C, 60.85; H, 10.24.

2(*R*)-(2,2-Dimethoxyethyl)-3(*R*)-(1-methyl-1,3-butadienyl)-6(*R*)−[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-dihydro-6*H*-pyran (10). To a 1.0 M solution of vinylmagnesium bromide in THF (4 mL, 4 mmol) cooled to −78 °C and stirred under nitrogen was added dropwise the aldehyde **9** (514 mg, 1.38 mmol) in dry THF (6 mL). After 20 min the mixture was quenched with saturated $NaHCO_3$ and extracted with ether. After the usual workup, the crude product was flash chromatographed (AcOEt/EP 1/4) to afford 450 mg (81.5%) of mixture of alcohols as colorless oil.

To a stirred solution of above alcohols (9.7 g, 24.25 mmol) in CH_2Cl_2 (19 mL) and dry pyridine (8 mL) was added at 0 °C a solution of acetyl chloride (6.9 mL, 97 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred for 30 min at 0 °C and then allowed to warm to room temperature, and the excess of AcCl was hydrolyzed by addition of water. Extraction with ether and usual workup gave a residue which was purified by flash chromatography to give 10.3 g (93%) of acetates followed by 0.48 g of starting alcohols.

The above mixture of acetates (6 g, 13.6 mmol) in THF (35 mL) was heated in the dark with tetrakis(triphenylphosphine) palladium (1.25 g, 1.08 mmol) at 75 °C for 24 h. After cooling, water was added and the mixture was extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (AcOEt/EP 1/19) to give 4.68 g (90%) of the diene **10** as a separable 2/1 mixture of isomers E and *Z*. Analysis and spectral data of the major isomer: R_f 0.40 (AcOEt/EP 1/19); IR 3080, 1641 cm^{-1}; ^1H NMR (400 MHz) δ 6.57 (dt, J = 16.8, 10.5, 1H) 5.93 (d, J = 10.3, 1H), 5.86 (dt, J = 10.3, 2.5, 1H), 5.70 (dt, J = 10.4, 2.4, 1H), 5.13 (dd, J = 16.8, 1.7, 1H), 5.05 (dd, J = 10.4, 1.5, 1H), 4.62 (dd, J = 8.3, 3.2, 1H), 4.17 (m, 1H), 3.80 (m, 1H), 3.78 (dd, J = 10, 5.8, 1H), 3.65 (dd, J = 10, 5.8, 1H), 3.33 (s, 6H), 2.61 (m, 1H), 1.87 (ddd, J = 14.2, 8.5, 3.0, 1H), 1.73 (ddd, J = 14.2, 8.3, 3.2, 1H), 1.72 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100.6 MHz) δ 138.6 (C), 133.2 (CH), 129.3 (CH), 129.0 (CH), 127.5 (CH), 116.0 (CH_2), 102.90 (CH), 72.8 (CH), 69.2 (CH), 65.7 (CH_2), 53.3 (CH_3), 53.2 (CH_3), 50.0 (CH), 37.3 (CH_2), 26.1 (3 CH_3), 18.5 (C), 14.8 (CH_3), −5.1 (2 CH_3); MS (CI, NH_3) m/z (%): 400(4) $(M + NH_4)^+$, 383(2), 368(3), 351(100), 336(21), 319(11), 279(5), 219(14).

2(*R*)-(2-Oxoethyl)-3(*R*)-(1-methyl-1,3-butadienyl)-6(*R*)−[[(*tert*-butyldimethylsilyl)oxy] methyl]-2,3-dihydro-6*H*-pyran (11a). To a solution of **10** (1.0 g, 2.97 mmol) in THF (25 mL) cooled to 0 °C was added dropwise 60% aqueous trifluoroacetic acid (TFA) (16 mL) and the mixture stirred for 20 h at room temperature. Excess TFA was neutralized by careful addition of solid $NaHCO_3$, and the reaction mixture was extracted with ether (10 × 25 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed. Flash chromatography (AcOEt/EP 1/2 then 1/1) of the resultant residue gave 513 mg (78%) of **11a** as a 1/2 mixture of isomers. Analysis and spectral data of the major isomer: Rf 0.35 (AcOEt/EP 1/2); IR 3592, 1727 cm^{-1}; ^1H NMR (400 MHz) δ 9.76 (s, 1H), 6.60 (dt, J = 16.9, 10.4, 1H), 5.97 (d, J = 10.6, 1H), 5.78 (m, 1H), 5.71 (m, 1H), 5.19 (d, J = 16.5, 1H), 5.11 (d, J = 10.3, 1H), 4.27−4.20 (m, 3H), 3.84 (dd, J = 12.0, 9.4, 1H), 3.59 (dd, J = 11.9, 3.0, 1H), 2.77−2.71 (m, 3H), 1.69 (s, 3H); ^{13}C NMR (100.6 MHz) δ 201.1 (C),

136.7 (C), 132.5 (CH), 129.8 (2 CH), 126.1 (CH), 117.2 (CH_2), 73.9 (CH), 64.6(CH), 62.8 (CH_2), 49.4 (CH 47.0 (CH_2 14.4 (CH_3).

2(*R*)-(2-Oxoethyl)-3(*R*)-(1-methyl-1,3-butadienyl)-6(*R*)-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-2,3-dihydro-6*H*-pyran (11b). To a solution of **11a** (1.27 g, 5.7 mmol) in 300 μL of CH_2Cl_2 at 0 °C was added triethylamine (2.75 mL), (dimethylamino)pyridine (DMAP) (48 mg, 0.39 mmol), followed by *tert*-butyldiphenylsilyl chloride (TBDPSCl) (1.638 mL, 6.3 mmol). The reaction mixture was stirred at room temperature for 36 h and then hydrolyzed with water (5mL) and extracted with ether. The combined organic layers were washed with brine and dried, and the solvent was removed under reduced pressure. Flash chromatography (AcOEt/EP 1/19) of the resultant residue furnished 2.58 g (98%) of aldehyde **11b** as a 2/1 (order of elution) separable mixture of isomers. Analysis and spectral data of the major isomer: R_f 0.4 (two elutions AcOEt/EP 1/19); IR 3072, 1729 cm^{-1}; ^1H NMR (400 MHz) δ 9.76 (t, J = 2.2, 1H), 7.74−7.69 (m, 4H), 7.46−7.37 (m, 6H), 6.58 (dt, J = 16.6, 10.5, 1H), 5.98−5.90 (m, 2H), 5.76 (dt, J = 10.5, 2.0, 2.0, 1H), 5.18 (d, J = 16.6, 1H), 5.1 (d, J = 10.5, 1H), 4.31−4.21 (m, 2H), 3.82 (d, J = 2, 1H), 3.79 (s, 1H), 2.73 (m, 1H), 2.55 (m, 2H), 1.70 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100.6 MHz) δ 201.1 (C), 137.1 (C), 135.6 (4 CH), 132.5 (2 C), 129.7 (2 CH), 128.9 (2 CH), 127.7 (4 CH), 116.8 (CH_2), 73 (CH), 68.5 (CH), 65.8 (CH_2), 49.4 (CH), 47.3 (CH_2), 26.8 (3 CH_3), 19.2 (C), 14.6 (CH_3); MS (CI, NH_3) m/z (%): 478(100) $(M + NH_4)^+$, 461(4), 383(76), 351(11), 305(14), 196(8), 187(21), 133(5), 78(23).

1-[6(*R*)-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,6-dihydro-3(*R*)-(1-methyl-1,3-butadienyl)-2*H*-pyran-3-yl]-3-pentyn-2-one (14). To a stirred solution of *Z*/*E* 1-bromopropene (160 μL, 1.85 mmol) in dry THF (1.5 mL) under nitrogen at −78 °C was added dropwise 1.6 M solution of n-BuLi in hexane (1.5 mL, 2.4 mmol). The resultant milky mixture was stirred at −78 °C for 2 h before a solution of **11b** (0.46 g, 1 mmol) in THF (2 mL) was slowly added. The reaction mixture was stirred for an additional 1 h at −78 °C and then allowed to warm to 0 °C. A saturated aqueous solution of NH_4Cl was added, and the product was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash chromatography of the residue (AcOEt/PE 5/95 and 10/90) gave 443 mg (88%) of mixture of alcohols as colorless oil.

Treatment of this product with Dess−Martin periodinane (600 mg) in CH_2Cl_2 (5 mL) for 45 min at room temperature as indicated above afforded after flash chromatography (AcOEt/PE 5/95) 60 mg of the minor isomer, 52 mg of the mixture of isomers, and 231 mg of the major isomer (78% combined yield). Analysis and spectral data of the major isomer: IR 1677 cm^{-1}; ^1H NMR (400 MHz) δ 7.74−7.68 (m, 4H), 7.45−7.38 (m, 6H), 6.56 (dt, J = 17, 10.5, 1H), 6.02 (dt, J = 10.3, 2.3, 1H), 5.94 (d, J = 10.8, 1H), 5.74 (dt, J = 10.3, 2.0, 1H), 5.15 (dd, J = 16.7, 1.5, 1H), 5.08 (d, J = 10.5, 1H), 4.3-4.25(m, 2H), 3.82 (dd, J = 10.1, 5.6, 1H), 3.74 (dd, J = 10.1, 6.9, 1H), 2.7-2.66 (m, 3H), 1.83 (s, 3H), 1.7 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100.6 MHz) δ 185.0 (C), 137.6 (C), 135.6 (4 CH), 132.7 (CH), 129.7 (2 C and CH), 129.1 (CH), 128.1 (CH), 127.7 (4 CH), 116.6 (CH_2), 94.4 (C), 80.4 (C), 72.5 (CH), 69.4 (CH), 65.7 (CH_2), 49.3 (CH and CH_2), 26.8 (3 CH_3), 19.2 (C), 14.4 (CH_3), 3.9 (CH_3); MS (CI, NH_3) m/z (%): 516(100) $(M + NH_4)^+$, 499(11), 421(25), 316(10), 274(16), 256(10), 196(25), 190(23), 134(30), 118(49), 78(43); $[\alpha]_D$ −86° (c 3.7, $CHCl_3$). Anal. Calcd for $C_{32}H_{38}O_3Si$: C, 77.06; H, 7.68. Found C, 77.11; H, 7.77.

Intramolecular Diels−Alder Reaction of 14. Naphthopyranones 18a and 19a. A solution of **14** (155 mg, 0.31 mmol) and few crystals of hydroquinone in degassed toluene under Ar (6 mL) were heated in a sealed Pyrex tube for 24 h at 200 °C. After cooling, the toluene was evaporated under reduced pressure and the residue flash chromatographed (AcOEt/PE 5/95) to give 64 mg (41%) of **18a** followed by 46 mg of **19a** (30%).

18a: colorless oil; R_f = 0.5 (AcOEt/EP 1/9); IR 1696 cm^{-1}; ^1H NMR (400 MHz) δ 7.70−7.68 (m, 4H), 7.45−7.39 (m, 6H), 6.11 (d, J = 10.5, 1H, H-11), 5.93 (dt, J = 9.6, 1.8, 1H, H-1), 5.92 (dt, J = 10.5, 2.8, 1H, H-12), 5.70 (dt, J = 10.1, 3.3, 1H, H-2), 4.35 (m, 1H, H-13), 3.90 (ddd, J = 12.1, 9.6, 5.1, 1H, H-8), 3.74 (d, J = 6 2, 2H, H-14), 2.80 (dd, J = 13.9, 5.1, 1H), 2.79 (dd, J = 22.0, 1H), 2.67 (dd, J = 23.0, 4.0, 1H), 2.49 (dd, J = 13.9, 12.1, 1H), 2.39 (ddd, J = 9.5, 4.4, 2.7, 1H), 1.88 (s, 3H,Me-4), 1.06(s, 9H), 0.83(s, 3H, Me-10); ^{13}C NMR (100.6 MHz) δ 204.2 (C), 137.3 (C), 136.2 (C), 135.6 (4 CH), 133.4 (C), 130.7 (CH), 129.8 (2 CH), 128.9 (CH),127.7 (4 CH), 126.2 (CH), 121.7 (CH), 74.5 (CH), 67.9 (CH), 65.7 (CH_2), 49.3 (CH_2), 47.0 (CH), 37.8 (C), 33.7 (CH_2), 26.8 (3 CH_3), 22.8 (CH_3), 20.3 (CH_3), 19.2(C); MS (CI, NH_3) m/z (%) 516(75) $(M + NH_4)^+$, 499(77), 421(43), 311(21), 225(8), 133(100), 102(70), 85(60); $[\alpha]_D$ −22° (c 5.8, $CHCl_3$).

19a: colorless oil; R_f = 0.4 (AcOEt/EP 1/9); IR 1693 cm^{-1}; 1H NMR (400 MHz) δ 7.7−7.65 (m, 4H), 7.44−7.35,(m, 6H), 6.08 (d, J = 10.5, 1H, H-11), 5.98 (dt, J = 10.5, 3.0, 1H, H-1), 5.93 (dd, J = 9.6, 3.0, 1H, H-12), 5.75 (ddd, J = 9.5, 5.0, 2.0, 1H, H-2), 4.36 (m, 1H, H-13), 3.74 (d, J = 5.6, 2H, H-14), 3.63 (td, J = 10.5, 6.0, 1H, H-8), 2.77 (d, J = 18.0, 1H), 2.67 (d, J = 20, 1H), 2.63 (dd 18.0, 10.5, 1H), 2.31 (dd, J = 10.0, 6.0, 1H), 2.08 (dd, J = 10.5, 2.0 1H), 1.89 (s, 3H, Me-4), 1.09 (s, 3H, Me-10) 1.04(s, 9H); ^{13}C NMR (100.6 MHz) δ 202.9 (C); 137.9 (C); 135.6 (4 CH); 133.4 (C); 131.8 (CH); 129.6 (2 C); 127.6 (CH); 125.9 (CH); 125.0 (CH); 73.4 (CH); 65.7 (CH); 65.2 (CH_2); 47.4 (CH_2); 46.8 (CH); 41.5 (C); 34.2 (CH_2); 28.0 (CH_3); 26.8 (3 CH_3); 20.0 (CH_3); 19.2 (C); MS (CI, NH_3) m/z (%): 516(6) $(M + NH_4)^+$, 499(8), 421(38), 287(7), 225(7), 133(100), 102(5); $[\alpha]_D$ −107° (c 6.2, $CHCl_3$).

Addition of Methyl Copper Reagent to α,β-Unsaturated Ketone 18a. Compound 17. To a stirred suspension of CuI (150 mg, 0.79 mmol) in dry ether (0.5 mL) under nitrgen cooled to −40 °C was added dropwise a 1.6 M solution of MeLi in ether (450 μL, 0.72 mmol). After being stirred for 15 min at −40 to −30 °C, the mixture was cooled to −78 °C, BF_3−Et_2O (100 μL) was added followed by a solution of **18a** (50 mg, 0.10 mmol) in ether (0.5 mL). The reaction mixture was allowed to warm to −30 °C during 1.5 h, recooled to −70 °C, and then quenched with water with vigorous stirring. The dry ice−acetone bath was removed, and the temperature was allowed to rise to ambient temperature. The mixture was filtered through Celite with suction, and the filter cake was rinsed with ether. The filtrate was tranferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent was removed using a rotary evaporator. The resultant oily residue was purified by flash chromatography (AcOEt/PE 5/95) to afford 32 mg (62%) of **17** as colorless oil. IR 1721 cm^{-1}; ^1H NMR (400 MHz) δ 0.83 (s, 3H), 1.06 (s, 9H), 1.09 (s, 3H), 1.15 (s, 3H), 1.76 (dd, J = 17.5, 5.5, 1H), 1.94 (br d, J = 17.5, 1H), 2.29 (br d, j = 9, 1H), 2.53 (t, J = 12, 1H), 2.54 (s, 1H, H-5), 2.64 (dd (J = 12, 5.5, 1H), 3.73 (d, J = 5, 2H), 3.79−3.85 (m, 1H, H-8), 4.35−4.37 (m, 1H, H-13), 5.60−5.64 (m, 1H, H-2), 5;88−5.93 (m, 2H, H-1 and H-12), 6.15 (br d, J = 10, 1H, H-11), 7;38−7.44 (m, 6H), 7.67−7.70 (m, 4H); ^{13}C NMR (50.3 MHz) δ 17.8 (CH_3), 19;3 (C), 23.4 (CH_3), 26.9 ($3CH_3$), 30.5 (CH_3), 38.8 (C), 39.4 (C), 42.7 (CH2), 50.0 (CH), 64.3 (CH), 66.0 (CH_2), 70.7 (CH), 75.1 (CH), 124.9 (CH), 126.7 (CH), 127.8 (4CH), 129.0 (CH), 129.9 (2CH), 133.5 (2C), 135.7 (4CH), 207.7(C); $[\alpha]_D$ −75° (c 6.2, $CHCl_3$). $[\alpha]_D$ −75° (c 6.2, $CHCl_3$). Anal. Calcd for $C_{33}H_{42}O_3Si$: C, 77.04; H, 8.17. Found C, 77.12; H, 8.22.

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Supporting Information Available: Experimental procedures including synthesis and characterization of compounds **12, 15, 18b, 19b, 20−23**, NMR spectra of **14** and **17**, 2D NOESY spectra of **18b** and **19b**, and the X-ray crystal data for compound **22b** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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