II (DEC, VMS) computer. Final convergence was reached at $R = 0.041$, $R_w = 0.037$. The maximum noise level in the final difference Fourier was 0.16 e Å^{-3}. The bond lengths and angles differed in no substantial detail from those revealed by the first determination. Structure factor data from both laboratories and detailed tables of the molecular dimensions are available as supplementary material.

Acknowledgment. We thank Dr. Andrew Mott (Minnesota 3M Co., Harlow, Essex) for the PPP calculations described in the text. The work was supported in part by the U.K. Science and Education Research Council, the Belgian organization IWONL, and the Belgian National Lottery. Agfa-Gavaert N.V. are thanked for their support and for permission to publish. We acknowledge also the interest of Dr. J. J. Jennen in this work.

Registry No. 1, 7364-25-2; **7a**, 134905-26-3; **7b**, 134905-27-4; **7c**, 134905-28-5; **7d**, 134905-29-6; **7e**, 134905-30-9.

Supplementary Material Available: Tables of crystallographic data and positional parameters from both research groups; ^{1}H (at 90 MHz) and ^{13}C NMR spectra (22.5 MHz) for compound **7b** (7 pages). Ordering information is given on any current masthead page. Tabulated F values are filed with the Cambridge Crystallographic Data Centre.

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A Novel Approach to Angular Triquinanes via Intramolecular 1,3-Dipolar Cycloaddition of Nitrile Oxide

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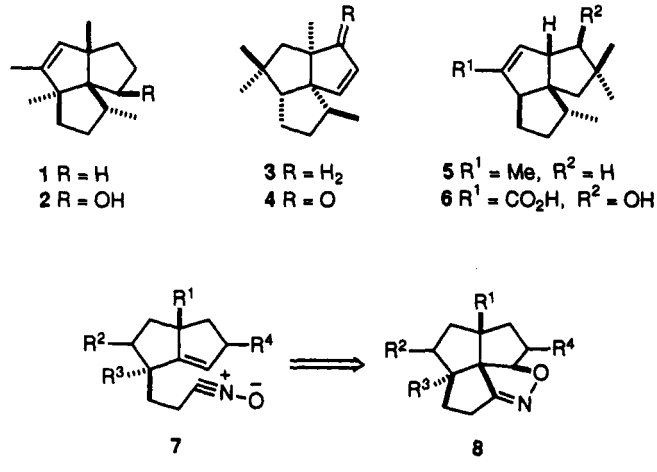
The framework of angular triquinane sesquiterpenes was stereoselectively constructed via the intramolecular 1,3-dipolar cycloaddition of nitrile oxide precursors. Optically active indandione **9** was converted into olefinic oximes **18A** and **18B** through two successive alkylations, followed by ring contraction. Oxidation of the mixture **18A** and **18B** with sodium hypochlorite gave rise to tetracyclic isoxazolines **21A** and **21B**, which were transformed into tricyclo[6.3.0.0^{4,8}]undecanes **28** and **29**.

Introduction

Angular-type triquinane sesquiterpenes, represented by isocomene (**1**), silphinene (**3**), and pentalenene (**5**), have received a great deal of attention from synthetic chemists due to their unique architectural features.[1] Recently we synthesized (±)-3-oxosilphinene (**4**) via intramolecular Diels-Alder reaction[2] and (±)-pentalenene (**5**) and (±)-pentalenic acid (**6**) via an intramolecular double Michael reaction (Scheme I).[3] It was considered that the intramolecular 1,3-dipolar cycloaddition of nitrile oxide **7** giving tetracyclic isoxazoline **8** could provide an useful route to angular triquinanes. Although extensive studies of 1,3-dipolar cycloadditions have been carried out,[4] few examples of construction of spiro ring systems using intramolecular 1,3-dipolar cycloadditions of nitrile oxides or nitrones have been recorded.[5] The 1,3-dipolar cycloaddition of nitrile oxide **7**, which could be prepared from the optically active indandione **9**,[6] was thus investigated. We wish to report

Scheme I



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(4) (a) Curran, D. P., Ed. *Advances in Cycloaddition*; JAI Press: Greenwich, 1988; Vol. 1. (b) Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH: New York, 1988, pp 433-437.

(5) (a) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 6291. (b) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (c) Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 1845.

(6) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675.

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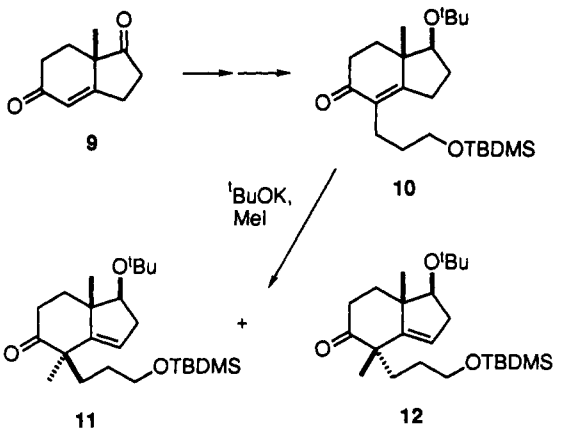
Scheme II



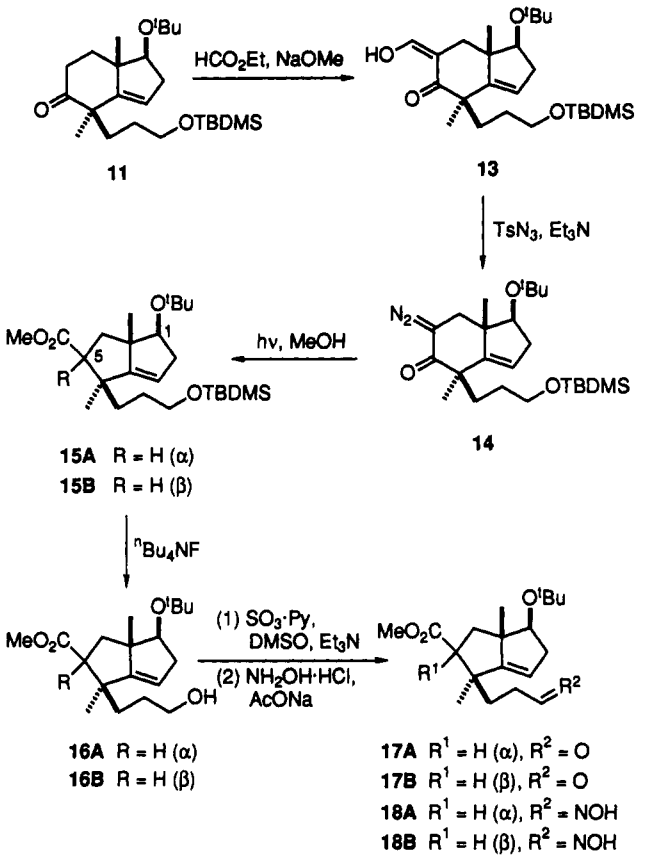
a highly stereocontrolled assembly of the angular tricyclopentanoid skeleton and the synthesis of a potential intermediate (**29**) of isocomene (**1**)[7,8] and 1-hydroxyisocomene (**2**).[9]

Synthesis of a Substrate for 1,3-Dipolar Cycloaddition. According to the previous procedure,[10] the optically active indandione **9**[6] was converted into enone **10**, which was subjected to methylation (Scheme II). Treatment of **10**[10] with methyl iodide in the presence of potassium *tert*-butoxide[11] in dimethylformamide at −60 to −40 °C gave a mixture of two methylated compounds (**11** and **12**) in 86% yield in a 3.8:1 ratio. The major product was expected to be the α-methylated compound **11** because methylation should occur mainly from the less hindered α-side of **10**.[11] Separation of the two diastereoisomers was performed by HPLC and the major component **11** converted into a substrate for the 1,3-dipolar cycloaddition.

Ring contraction of the cyclohexanone moiety of **11** was next carried out (Scheme III). Formylation of **11**, followed by diazo exchange of **13**, provided diazo compound **14**. This material was subjected to Wolff rearrangement, carried out by irradiation with a high-pressure mercury lamp in methanol. The product, obtained in 53% overall yield from **11**, was composed of two diastereoisomers (**15A** and **15B**) in a ratio of ca. 2:1. The methine hydrogens at the C-1 and C-5 positions of the major product **15A** resonated at higher fields (3.70 and 2.53 ppm) relative to those in the minor isomer **15B** (3.92 and 3.09 ppm) in the ^{1}H NMR spectrum. This was ascribed to anisotropic effects of the ester group and the olefin which indicated that the methoxycarbonyl group of **15A** was β-oriented.

The *tert*-butyldimethylsilyl group of the mixture of **15A** and **15B** was removed by treatment with tetra-*n*-butylammonium fluoride. The resulting mixture of alcohols,

Scheme III



16A and **16B**, obtained in 94% yield, was oxidized with dimethyl sulfoxide and sulfur trioxide–pyridine complex in the presence of triethylamine[12] to give a mixture of aldehydes **17A** and **17B**, which was condensed with hydroxylamine. The desired oximes **18A** and **18B** were obtained in 95% overall yield as a mixture of syn and anti isomers and used as such in the following key reaction.

1,3-Dipolar Cycloaddition of Olefinic Nitrile Oxide. The 2:1 mixture of oximes **18A** and **18B** was oxidized with 6% aqueous sodium hypochlorite[13] in dichloromethane at room temperature. The intramolecular cycloaddition smoothly occurred under the same reaction conditions to produce separable isoxazolines **21A** and **21B** in 96% yield in a 2:1 ratio (Scheme IV). Their epimeric relationship at C-3 was supported by the equilibration between **21A** and **21B** on treatment with sodium methoxide. The configurations **21A** and **21B** of two products were deduced from the consideration of reaction mechanism.[14]

The 3.8:1 mixture of two methyl compounds **11** and **12** was transformed, without separation, according to the same procedure as above, into a mixture of oximes **18** and **23**, which was treated with 6% aqueous sodium hypochlorite as above to afford only the above products **21A** and **21B**. Thus the tedious separation of **11** and **12** using HPLC techniques became unnecessary. It is believed that no formation of isomers **22**, **26**, and **27** is observed because they necessitate either a prohibitively strained transition state (**20**, **24**, or **25**) (e.g., entailing formation of a trans

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(9) Isolation: Bohlmann, F.; Zdero, C. *Phytochemistry* **1981**, *20*, 2529.

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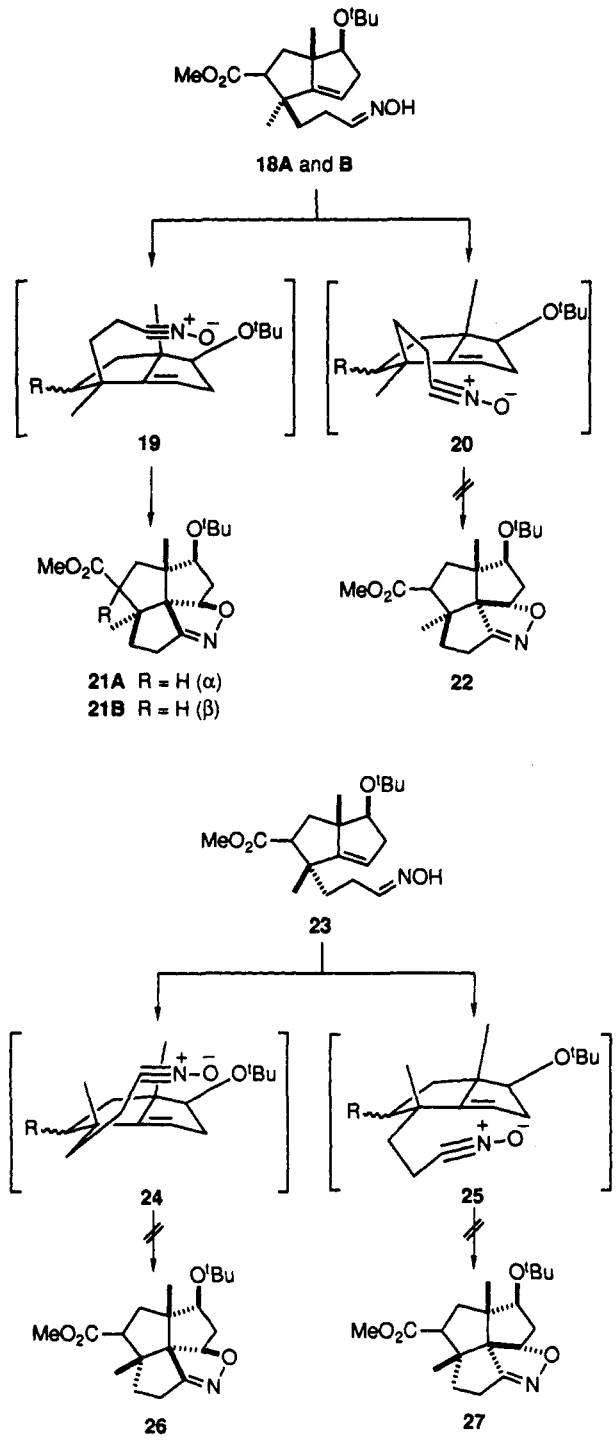
(12) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(13) (a) Zang, Y.; O'Conner, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5590. (b) Lee, G. A. *Synthesis* **1982**, 508.

(14) (a) Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081. (b) Murthy, K. S. K.; Hassner, A. *Tetrahedron Lett.* **1987**, *28*, 97. (c) Shishido, K.; Tokunaga, Y.; Omachi, N.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1093; (d) *J. Chem. Soc., Perkin Trans. 1* **1990**, 2481.

Scheme IV

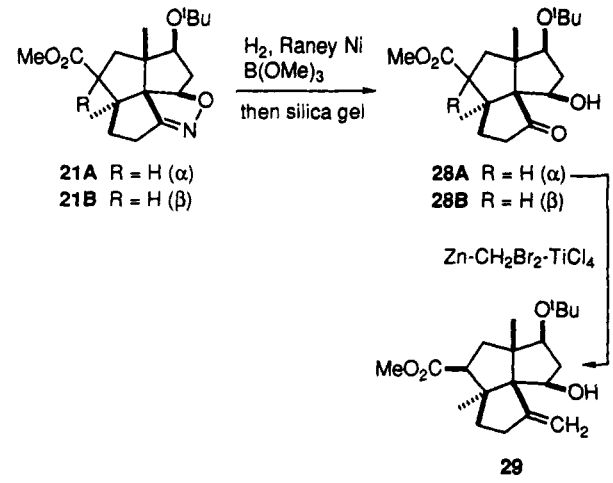


[3.3.0]bicyclo ring system) or an approach from the crowded concave face of the extant bicyclo ring system.

The 2:1 mixture of isoxazolines **21A** and **21B** was reduced with W-2 Raney nickel and trimethyl borate[15] under a hydrogen atmosphere, and the products were treated with silica gel in order to complete the hydrolysis of the resulting imines (Scheme V). A mixture of β-hydroxy ketones **28A** and **28B** was obtained in 83% yield in a ratio of 2:1. The major component **28A**, mp 126–127 °C; $[\alpha]^{28}_D$ + 96° (*c* 0.86, $CHCl_3$), was purified by recrystallization from hexane. The structure of **28A** was determined by X-ray analysis (Figure 1). The ketone **28A** was transformed into the olefin **29** in 37% yield by the Nozaki–

(15) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

Scheme V



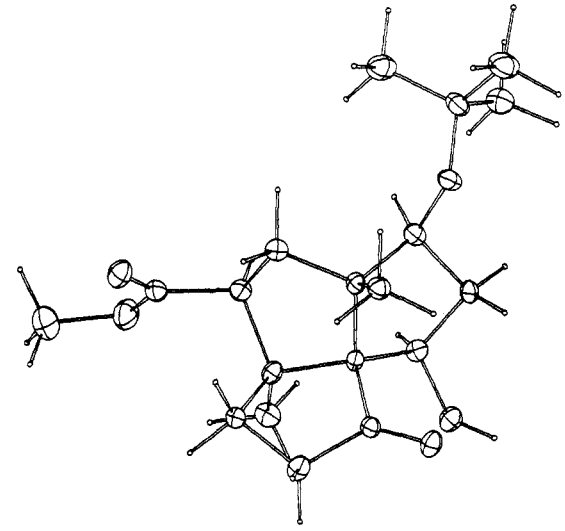


Figure 1. ORTEP of the X-ray crystal structure of **28A**.

Lombardo method.[16] Thus the synthesis of the framework of angular triquinanes carrying all of the carbons present in isocomene (**1**) and 1-hydroxyisocomene (**2**) has been accomplished.

Experimental Section

General. All reactions except hydrogenations were carried out under a positive atmosphere of dry N_2 or Ar. Ether and THF were distilled from Na–benzophenone. CH_2Cl_2 was distilled from P_2O_5 and kept over 4-Å molecular sieves. DMSO and DMF were distilled from CaH_2 and kept over 4-Å molecular sieves. *t*-BuOH was distilled from Na and kept over 4-Å molecular sieves. Et_3N was distilled from KOH and stored over KOH. NaH in mineral oil was washed with hexane three times prior to use. All extracts were dried over $MgSO_4$. Silica gel chromatography was carried out with Merck kieselgel 60 (Art. No. 7734 or 9387). HPLC was performed on a Gilson HPLC system equipped with a 10 × 250 mm column of Dynamax microsorb silica (5 μm) and monitored by using UV and refractive index detectors. NMR spectra were taken in $CDCl_3$.

(+)-(1*S*,4*R*,7a*S*)-1-*tert*-Butoxy-4-[3-(*tert*-butyldimethylsiloxy)propyl]-4,7a-dimethyl-2,4,7,7a-tetrahydro-5-(6*H*)-indanone (11). A solution of enone **10**[10] (6.77 g, 17.5 mmol) in dry DMF (20 mL) was slowly added during 40 min at room temperature to a stirred solution of freshly prepared *t*-BuOK (3.37 g, 33.2 mmol) in dry DMF (50 mL). The mixture was stirred for

(16) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417. (b) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.
(17) Jia-Xing, Y. *Acta Crystallogr., Sect. A* **1981**, *37*, 642; **1983**, *39*, 35.

1.5 h at room temperature, and MeI (4.72 g, 33.2 mmol) was then added dropwise at −60 °C. After being stirred for 10.5 h at −40 °C and addition of saturated aqueous NH_4Cl, the resulting mixture was thoroughly extracted with ether. The extract was washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with hexane–AcOEt (100:3), to give a mixture of ketones **11** and **12** (6.01 g, 86%) as a colorless oil in a 3.8:1 ratio. Further purification of the mixture by HPLC with hexane–ether (95:5) as eluant afforded the pure ketone **11** as a colorless oil: $[\alpha]^{28}_D$ +21° (*c* 1.27, $CHCl_3$); IR (neat) 1715 (C=O), 1625 (C=C) cm^{-1}; ^1H NMR (500 MHz) δ 0.01 (s, 6 H), 0.86 (s, 9 H), 1.13 (s, 3 H), 1.15 (s, 3 H), 1.16 (s, 9 H), 1.33–1.76 (m, 5 H), 1.85 (ddd, 1 H, *J* = 13.0, 6.5, 6.5 Hz), 2.24–2.38 (m, 3 H), 2.63 (ddd, 1 H, *J* = 15.9, 11.1, 5.7 Hz), 3.55 (t, 2 H, *J* = 6.3 Hz), 3.75 (dd, 1 H, *J* = 9.5, 7.4 Hz), 5.37 (dd, 1 H, *J* = 3.4, 1.5 H); MS *m/z* 408 (M^+). Anal. Calcd for $C_{24}H_{44}O_3Si$: C, 70.53; H, 10.85. Found: C, 70.44; H, 10.89.

(+)-(1*S*,4*S*,5*S*,6a*S*)- (15A) and (1*S*,4*S*,5*R*,6a*S*)-1-*tert*-Butoxy-4-[3-(*tert*-butyldimethylsiloxy)propyl]-4,6a-dimethyl-1,2,4,5,6,6a-hexahydro-5-(methoxycarbonyl)pentalene (15B). After addition of MeOH (0.07 mL, 17.3 mmol) to a suspension of NaH (60% in oil, 59 mg, 1.48 mmol) in dry ether (1.0 mL) at 0 °C, the mixture was stirred for 30 min at 0 °C. To this mixture were added at 0 °C a solution of **11** (97.4 mg, 0.247 mmol) in dry ether (2 mL) and, after 6 min, ethyl formate (0.365 g, 4.93 mmol). The mixture was stirred for 15 min at 0 °C and then for 4 h at room temperature. After addition of saturated aqueous NH_4Cl, the resulting mixture was thoroughly extracted with ether. The extract was washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure to give a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (95:5) provided hydroxymethylene derivative **13** (88.7 mg) as an oil: IR (neat) 1650 (C=O) cm^{-1}; ^1H NMR (90 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 0.90 (s, 3 H), 1.19 (s, 3H), 1.22 (s, 9 H), 1.32–2.45 (m, 8 H), 3.57 (t, 2 H, *J* = 6.1 Hz), 3.79 (t, 1 H, *J* = 2.4 Hz), 5.40 (t, 1 H, *J* = 2.4 Hz), 7.79 (d, 1 H, *J* = 7.3 Hz), 14.64 (d, 1 H, *J* = 7.3 Hz); MS *m/z* 437 ($M^+ + 1$).

To a stirred solution of the above hydroxymethylene derivative **13** (88.7 mg) in dry CH_2Cl_2 (1.0 mL) were added at 0 °C Et_3N (62.0 mg, 0.610 mmol) and a solution of tosyl azide (80.0 mg, 0.407 mmol) in dry CH_2Cl_2 (1.6 mL), and the mixture was stirred for 10 min at 0 °C and then for 2.5 h at room temperature. After addition of saturated aqueous NH_4Cl at 0 °C, the resulting mixture was thoroughly extracted with ether. The extract was washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure to afford a residue, which was purifed by chromatography on silica gel. Elution with hexane–AcOEt (9:1) yielded diazo compound **14** (77.7 mg) as an oil: IR (neat) 2080 (N=N), 1645 (C=O), 1625 (C=C) cm^{-1}; ^1H NMR (90 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 1.09 (s, 3 H), 1.19 (s, 9 H), 1.21 (s, 3 H), 1.33–2.50 (m, 8 H), 3.56 (t, 2 H, *J* = 5.7 Hz), 3.84 (t, 1 H, *J* = 7.9 Hz), 5.44 (dd, 1 H, *J* = 2.6, 2.6 Hz); MS *m/z* 435 ($M^+ + 1$).

A solution of the above diazo compound **14** (77.7 mg) in MeOH (16 mL) was irradiated for 2.5 h at 0 °C with a 400-W high-pressure mercury lamp through a Pyrex filter. Evaporation of the solvent under reduced pressure gave a residue, which was chromatographed on silica gel, eluting with hexane–AcOEt (9:1), to afford a mixture of methyl esters **15A** and **15B** (55 mg, 53% overall yield from **11**) as a colorless oil in a 2:1 ratio: $[\alpha]^{27}_D$ +46° (*c* 1.10, $CHCl_3$); IR (neat) 1740 (C=O), 1655 (C=C), 1645 (C=C) cm^{-1}; ^1H NMR (500 MHz) δ 0.01 (s, 4 H), 0.02 (s, 2 H), 0.87 (s, 6 H), 0.89 (s, 3 H), 0.90 (s, 1 H), 1.04 (s, 1 H), 1.13 (s, 2 H), 1.16 (s, 6 H), 1.17 (s, 3 H), 1.22 (s, 2 H), 2.53 (dd, $^2/_3$ H, *J* = 10.1, 9.4 Hz), 3.09 (dd, $^1/_3$ H, *J* = 11.0, 7.4 Hz), 3.54 (t, $^4/_3$ H, *J* = 8.2 Hz), 3.60 (t, $^2/_3$ H, *J* = 8.2 Hz), 3.66 (s, 1 H), 3.68 (s, 2 H), 3.70 (dd, $^2/_3$ H, *J* = 8.6, 7.1 Hz), 3.92 (dd, $^1/_3$ H, *J* = 9.2, 7.8 Hz), 5.11–5.14 (m, $^1/_3$ H), 5.20–5.23 (m, $^2/_3$ H); MS *m/z* 438 (M^+); exact mass found M^+ 438.3148, $C_{25}H_{46}O_4Si$ requires 438.3131.

(+)-(1*S*,4*S*,5*S*,6a*S*)- (16A) and (1*S*,4*S*,5*R*,6a*S*)-1-*tert*-Butoxy-4,6a-dimethyl-1,2,4,5,6,6a-hexahydro-4-(3-hydroxypropyl)-5-(methoxycarbonyl)pentalene (16B). A solution of tetra-*n*-butylammonium fluoride in THF (1.0 M, 0.25 mL, 0.25 mmol) was added to a solution of the silyl ethers **15A** and **15B** (55.0 mg, 0.126 mmol) in THF (1.7 mL) at 0 °C. After being stirred for 10 h, concentration of the mixture under reduced pressure gave a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (7:3) provided alcohols **16A** and **16B** (38.4 mg, 94%) as a colorless oil in a 2:1 ratio: $[\alpha]^{27}_D$ + 67° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3630 (OH), 1725 (C=O), 1655 (C=C), 1645 (C=C) cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (s, 1 H), 1.10 (s, 1 H), 1.12 (s, 2 H), 1.16 (s, 6 H), 1.17 (s, 3 H), 1.24 (s, 2 H), 2.54 (dd, $^2/_3$ H, *J* = 10.4, 9.2 Hz), 3.11 (dd, $^1/_3$ H, *J* = 11.4, 9.2 Hz), 3.59 (dt, $^4/_3$ H, *J* = 6.4, 3.1 Hz), 3.65 (br t, $^2/_3$ H, *J* = 6.4 Hz), 3.67 (s, 1 H), 3.69 (s, 2 H), 3.71 (dd, $^2/_3$ H, *J* = 9.2, 6.8 Hz), 3.92 (dd, $^1/_3$ H, *J* = 9.4, 7.4 Hz), 5.14 (dd, $^1/_3$ H, *J* = 3.4, 1.6 Hz), 5.24 (dd, $^2/_3$ H, *J* = 4.0, 1.5 Hz); MS *m/z* 324 (M^+); exact mass found M^+ 324.2308, $C_{19}H_{32}O_4$ requires 324.2300.

(+)-(1*S*,4*S*,5*S*,6a*S*)- (18A) and (1*S*,4*S*,5*R*,6a*S*)-1-*tert*-Butoxy-4,6a-dimethyl-1,2,4,5,6,6a-hexahydro-4-[3-(hydroxyimino)propyl]-5-(methoxycarbonyl)pentalene (18B). A solution of sulfur trioxide–pyridine complex (60.0 mg, 0.38 mmol) in dry DMSO (1.0 mL) was added dropwise to a stirred solution of the alcohols **16A** and **16B** (38.4 mg, 1.19 mmol) and Et_3N (0.12 g, 1.19 mmol) in dry DMSO (1.0 mL) at room temperature. The mixture was stirred for 1.5 h at this temperature and then partitioned between ether and saturated aqueous NaCl. The aqueous layer was thoroughly extracted with ether. The combined ethereal layers were dried and evaporated under reduced pressure to give crude aldehydes **17A** and **17B** (54.5 mg) as an oil: IR ($CHCl_3$) 1730 (C=O), 1655 (C=O) cm^{-1}; ^1H NMR (90 MHz) δ 0.91, 1.05, 1.11, 1.17 and 1.23 (each s, 15 H), 3.00–4.00 (m, $^2/_3$ H), 3.68 (s, 1 H), 3.70 (s, 2 H), 3.92 (t, $^1/_3$ H, *J* = 8.3 Hz), 5.16 (dd, $^1/_3$ H, *J* = 3.0, 2.2 Hz), 5.28 (dd, $^2/_3$ H, *J* = 3.7, 2.2 Hz), 9.74 (t, $^2/_3$ H, *J* = 1.5 Hz), 9.80 (t, $^1/_3$ H, *J* = 1.6 Hz). The product was used in the next reaction without purification.

To a solution of the above aldehydes **17A** and **17B** (54.5 mg) in MeOH (1.2 mL) were added hydroxylamine hydrochloride (8.3 mg, 0.14 mmol) and sodium acetate (11.1 mg, 0.16 mmol), and the mixture was stirred for 2 h at room temperature. Evaporation of the solvent under reduced pressure gave a residue, which was taken up into $CHCl_3$. The organic solution was washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (3:2) as eluant to afford oximes **18A** and **18B** (37.8 mg, 95% overall yield) as a mixture of four isomers: IR ($CHCl_3$) 3590 (OH), 1730 (C=O), 1655 (C=N and C=C) cm^{-1}; ^1H NMR (500 MHz) δ 0.93, 1.05, 1.17, 1.24 and 1.26 (each s, 15 H), 1.33–2.70 (m, 9 H), 3.11 (t, $^2/_3$ H, *J* = 9.0 Hz), 3.56–4.26 (m, $^1/_3$ H), 5.11–5.33 (m, 1 H), 6.55–7.10 (m, $^1/_2$ H), 7.37 (t, 2 H, *J* = 5.9 Hz); MS *m/z* 337 (M^+); exact mass found M^+ − 57 281.1608, $C_{15}H_{23}NO_4$ requires 281.1589.

(+)-(1*S*,3*S*,4*S*,8*R*,11*S*)- (21A) and (1*S*,3*R*,4*S*,8*R*,9*R*,11*S*)-11-*tert*-Butoxy-1,4-dimethyl-3-(methoxycarbonyl)tricyclo[6.3.0.0^{4,8}]undecano[7,9-*cd*]isoxazole (21B). To a solution of oximes **18A** and **18B** (37.8 mg, 0.122 mmol) in CH_2Cl_2 (4.0 mL) was added at room temperature 6% aqueous NaOCl (0.21 mL, 0.168 mmol), and the mixture was stirred for 30 min at the same temperature. After dilution with CH_2Cl_2, the resulting mixture was washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure to give a residue, which was purified by chromatography on silica gel. Elution with hexane–AcOEt (4:1) afforded isoxazolines (36.0 mg, 96%) as a mixture of two diastereoisomers in a 2:1 ratio. HPLC separation with hexane–ether (7:3) as eluant provided the major product **21A** as a colorless solid. Recrystallization from hexane gave colorless needles, mp 77–78 °C: $[\alpha]^{22}_D$ +96° (*c* 0.86, $CHCl_3$); IR (neat) 1735 (C=O), 1635 (C=N) cm^{-1}; ^1H NMR (500 MHz) δ 1.03 (s, 3 H), 1.16 (s, 12 H), 1.67 (ddd, 1 H, *J* = 12.9, 9.5, 7.8 Hz), 1.77 (dd, 1 H, *J* = 13.6, 12.8 Hz), 1.94 (ddd, 1 H, *J* = 13.6, 11.5, 6.3 Hz), 1.99 (dd, 1 H, *J* = 13.6, 6.5 Hz), 2.26 (ddd, 1 H, *J* = 12.9, 11.9, 3.2 Hz), 2.32 (ddd, 1 H, *J* = 14.7, 11.9, 7.8 Hz), 2.42 (ddd, 1 H, *J* = 13.6, 8.2, 7.1 Hz), 2.53 (ddd, 1 H, *J* = 14.7, 9.5, 3.2 Hz), 2.63 (dd, 1 H, *J* = 12.8, 6.5 Hz), 3.44 (dd, 1 H, *J* = 11.5, 7.1 Hz), 3.71 (s, 3 H), 4.62 (dd, 1 H, *J* = 8.2, 6.3 Hz); ^{13}C NMR (125 MHz) δ 16.11, 22.96, 24.75, 28.51, 36.49, 37.89, 39.53, 50.07, 51.56, 53.21, 54.59, 72.88, 75.62, 83.09, 84.09, 167.28, 173.02; MS *m/z* 335 (M^+); exact mass found M^+ 335.2097, $C_{19}H_{29}NO_4$ requires 335.2097.

Further elution of HPLC gave the minor isomer **21B** as a solid, recrystallization of which from hexane provided colorless needles, mp 102.5–103 °C: $[\alpha]^{26}_D$ + 50° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 1730 (C=O), 1640 (C=N) cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (s, 3 H), 1.06 (s, 3 H), 1.15 (s, 9 H), 1.67 (ddd, 1 H, *J* = 12.7, 9.7, 7.9 Hz),

1.72 (dd, 1 H, J = 13.5, 6.1 Hz), 1.86 (dd, 1 H, J = 13.5, 10.4 Hz), 2.18 (ddd, 1 H, J = 15.0, 2.6, 2.4 Hz), 2.26 (ddd, 1 H, J = 15.0, 5.7, 5.2 Hz), 2.33 (ddd, 1 H, J = 12.7, 9.0, 2.4 Hz), 2.44 (ddd, 1 H, J = 14.4, 9.7, 9.0 Hz), 2.53 (ddd, 1 H, J = 14.4, 7.9, 2.4 Hz), 2.90 (dd, 1 H, J = 10.4, 6.1 Hz), 3.69 (s, 3 H), 3.90 (dd, 1 H, J = 5.7, 2.6 Hz), 4.78 (dd, 1 H, J = 5.2, 2.4 Hz); ^{13}C NMR (125 MHz) δ 18.80, 19.73, 23.30, 28.41, 39.91, 40.93, 41.08, 50.42, 51.56, 53.62, 57.89, 73.32, 78.23, 83.84, 89.50, 169.33, 173.80; MS m/z 335 (M^+). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.81; H, 8.71; N, 4.14.

(+)-(1*S*,3*S*,4*S*,8*S*,9*R*,11*S*)-11-*tert*-Butoxy-1,4-dimethyl-9-hydroxy-3-(methoxycarbonyl)-7-oxotricyclo[6.3.0.0^{4,8}]undecane (28A). The 2:1 mixture of isoxazolines **21A** and **21B** (102.0 mg, 0.304 mmol), W-2 Raney Ni (10 mg), and trimethyl borate (0.316 g, 3.04 mmol) in MeOH–H_2O (15:1; 4.8 mL) was stirred for 12.5 h at room temperature under H_2 (1 atm). After filtration through Celite, the filtrate was evaporated under reduced pressure to give a residue, which was partitioned between H_2O and $CHCl_3$. The aqueous layer was thoroughly extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl, dried, and evaporated under reduced pressure to give a residue, which was adsorbed on silica gel. After being allowed to stand overnight at room temperature, elution with hexane–AcOEt (7:3) afforded a mixture of β-hydroxy ketones **28A** and **28B** (83.5 mg, 83%) in a 2:1 ratio. Recrystallization of the product from hexane provided the major component **28A** as colorless needles, mp 126–127 °C: $[\alpha]^{28}_D$ +96° (c 0.86, $CHCl_3$); IR ($CHCl_3$) 3570 (OH), 1725 (C=O), 1670 (C=O) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (s, 3 H), 1.15 (s, 9 H), 1.28 (s, 3 H), 1.59 (ddd, 1 H, J = 13.8, 8.5, 2.6 Hz), 1.88–2.37 (m, 7 H), 2.40 (d, 1 H, J = 12.2 Hz; disappeared with D_2O), 2.68 (dd, 1 H, J = 12.4, 7.5 Hz), 3.34 (dd, 1 H, J = 11.5, 5.5 Hz), 3.72 (s, 3 H), 4.76 (ddd, 1 H, J = 12.2, 12.2, 5.6 Hz); MS m/z 338 (M^+). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.46; H, 9.00.

(+)-(1*S*,3*S*,4*S*,5*S*,7*R*,8*R*)-5-*tert*-Butoxy-1,4-dimethyl-7-hydroxy-2-(methoxycarbonyl)-9-methylidenetricyclo[6.3.0.0^{4,8}]undecane (29). To a suspension of Zn powder (14.5 g, 222 mg atom) and CH_2Br_2 (12.4 g, 7.12 mmol) in dry THF (100 mL) was added at −40 °C titanium(IV) tetrachloride (15.0 g, 79.3 mmol) during 8 min. The mixture (Lombardo's reagent) was stirred for 72 h at 5 °C and was used for the following reaction.

A solution of hydroxy ketone **28A** (17.5 mg, 0.052 mmol) in dry CH_2Cl_2 (1.0 mL) was added dropwise to the above Lombardo's reagent in dry THF (0.712 M, 0.25 mL, 0.178 mmol) at room temperature. After being stirred for 9 h at the same temperature, silica gel under ice cooling was added to the resulting mixture. After being stirred for 10 min at room temperature, the mixture was filtered through Celite. The filtrate and washings were combined and evaporated under reduced pressure to afford a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (17:3) gave olefin **29** (6.5 mg, 37%) as a colorless oil: $[\alpha]^{22}_D$ +11° (c 0.95, $CHCl_3$); IR ($CHCl_3$) 3650 (OH), 1730 (C=O), 1660 (C=C) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.84 (s, 3 H), 1.13 (s, 3 H), 1.16 (s, 9 H), 1.61–2.52 (m, 9 H), 2.58 (dd, 1 H, J = 12.5, 7.0 Hz), 3.39 (dd, 1 H, J = 11.3, 5.2 Hz), 3.69 (s, 3 H), 3.71–3.77 (m, 1 H); MS m/z 336 (M^+); exact mass found M^+ 336.2263, $C_{20}H_{32}O_4$ requires 336.2300.

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Supplementary Material Available: ^{1}H NMR spectra of compounds **15A** and **15B**, **16A** and **16B**, **18A** and **18B**, **21A**, and **29** and listing of bond lengths and angles and torsion angles and two independent molecular structures for **28A** (17 pages). Ordering information is given on any current masthead page.

Sequential Radical Ring Closure–Radical Ring Opening: Use in the Preparation of Benzofurans

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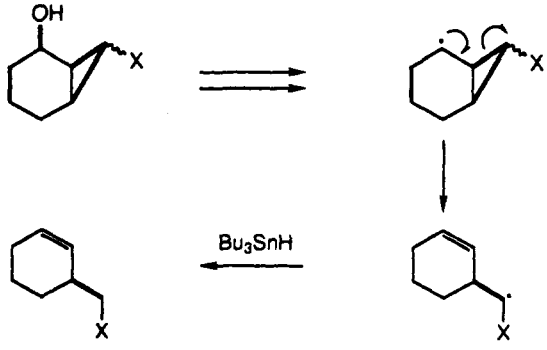
A radical ring closure–ring opening sequence (Scheme I) was used to prepare benzofuran derivatives.

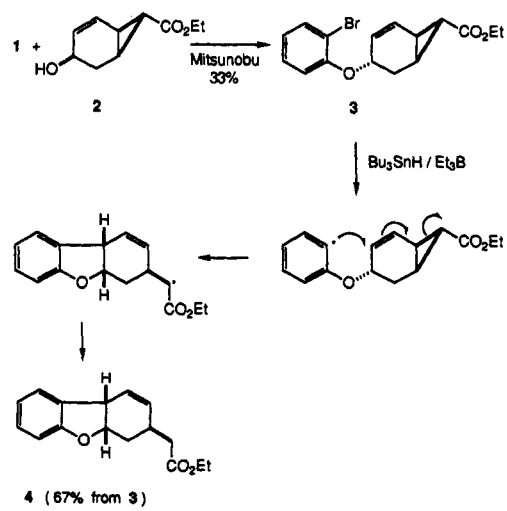
The radical ring opening sequence[1] of eq 1 (where X is, for example, H, alkyl, COOR, $CONMe_2$) represents a procedure for attaching alkyl and substituted-alkyl groups to cyclic structures. We have combined this methodology



Eq. 1

with conventional radical ring closure, as shown in Scheme I, in order to make several benzofuran derivatives required for evaluation as inhibitors[2] of leukotriene biosynthesis.

Scheme I



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