Synthesis of (±)-Bakkenolide-A and Its C-7, C-10, and C-7,10 Epimers by Means of an Intramolecular Diels−Alder Reaction

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(±)-Bakkenolide-A (**1**) was prepared in five steps from ethyl 4-benzyloxyacetoacetate by sequential alkylations with tiglyl bromide and (*Z*)-5-bromo-1,3-pentadiene, followed by an intramolecular Diels−Alder reaction of (*E*,*Z*)-triene **25b** as the key step. The hydrindane cycloadduct **28** was subjected to hydrogenation and spontaneous or acid-catalyzed lactonization, followed by a Witttig reaction to introduce the exocyclic methylene group of **1**. The known 7-epibakkenolide-A (**2**) and novel 10-epi- and 7,10-diepibakkenolide-A (**3** and **4**, respectively) stereoisomers were obtained as minor byproducts. When (*E*)-5-bromo-1,3-pentadiene was used instead of the *Z*-isomer, the 10-epi- and 7,10-diepibakkenolides were the major products. In both cases exo cyclization was preferred over endo. An alternative approach was based on a similar intramolecular Diels−Alder cycloaddition, using dimethyl malonate instead of ethyl 4-benzyloxyacetoacetate as the starting material for the double alkylation preceding the cycloaddition step. The cycloadduct was then converted into the corresponding α-phenylseleno propargyl esters **16** or **22**. However, attempted formation of the spiro center by a radical cyclization resulted chiefly in reductive deselenization.

Bakkenolide-A (**1**) is the simplest member of a family of sesquiterpene *β*-methylene spiro lactones that are formally related to the eremophilanes.[1] It was first isolated in 1968 from the wild butterbur *Petasites japonicus* by Woods and Kitahara et al.,[2] and independently by Naya et al.[3] Bakkenolide-A displays cytotoxicity against several carcinoma cell lines,[4] as well as insect antifeedant activity.[5] Several syntheses of **1**[6] and its congeners[7] have been reported. We recently prepared the 6-keto derivative of bakkenolide-A via a radical cyclization to establish the spiro lactone moiety, followed by an intermolecular high-pressure Diels−Alder reaction to construct the six-membered ring.[8] Unfortunately, poor stereoselectivity in the Diels−Alder step and difficulty in reducing the 6-keto group thwarted our attempts to prepare **1** by this method. We now report[9] a stereoselective new approach based on an intramolecular Diels−Alder reaction[10] that provided (±)-**1** as the principal product, along with smaller amounts of the known[7k] (±)-7-epibakkenolide-A (**2**) and novel (±)-10-epibakkenolide-A (**3**) and (±)-7,10-diepibakkenolide-A (**4**) analogues.

Results and Discussion

We first investigated the method indicated retrosynthetically in Scheme 1, where an intramolecular Diels−

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(1) For a review of bakkenolide-A and other sesquiterpene lactones, see: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2.

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(3) Naya, K.; Takagi, I.; Hayashi, M.; Nakamura, S.; Kobayashi, M.; Katsumura, S. *Chem. Ind. (London)* **1968**, 318. These authors referred to **1** as fukinanolide, an alternative name to bakkenolide A.

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(5) For example, see: (a) Harmatha, J.; Nawrot, J. *Biochem. Syst. Ecol.* **1984**, *12*, 95. (b) Nawrot, J.; Harmatha, J.; Novotný, L. *Biochem. Syst. Ecol.* **1984**, *12*, 99. (c) Nawrot, J.; Bloszyk, E.; Harmatha, J.; Novotný, L.; Drozdz, B. *Acta Entomol. Bohemoslov.* **1986**, *83*, 327. (d) Isman, M. B.; Brard, N. L.; Nawrot, J.; Harmatha, J. *J. Appl. Entomol.* **1989**, *107*, 524. (e) Nawrot, J.; Koul, O.; Isman, M. B.; Harmatha, J. *J. Appl. Entomol.* **1991**, *112*, 194.

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(7) For syntheses of some related products, see: homogynolide-A: (a) Hartmann, B.; Kanazawa, A. M.; Deprés, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 767. (b) Hartmann, B.; Kanazawa, A. M.; Deprés, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1993**, *34*, 3875. (c) Mori, K.; Matsushima, Y. *Synthesis* **1995**, 845. (d) Srikrishna, A.; Reddy, T. J. *Indian J. Chem.* **1995**, *34B*, 844; homogynolide-B: (e) Coelho, F.; Deprés, J.-P.; Brocksom, T. J.; Greene, A. E. *Tetrahedron Lett.* **1989**, *30*, 565. (f) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S. *Tetrahedron Lett.* **1994**, *35*, 429. (g) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069; palmosalide C: (h) Hartmann, B.; Deprés, J.-P.; Greene, A. E.; Freire de Lima, M. E. *Tetrahedron Lett.* **1993**, *34*, 1487; norbakkenolide-A: (i) Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun.* **1993**, 285; 4-epibakkenolide: (j) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 469; 7-epibakkenolide-A: (k) Srikrishna, A.; Reddy, T. J. *Tetrahedron* **1998**, *54*, 11517; 9-acetoxyfukinanolide: (l) Hamelin, O.; Deprés, J.-P.; Greene, A. E.; Tinant, B.; Declercq, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9992.

(8) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806.

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(10) For reviews of the intramolecular Diels−Alder reaction, see: (a) Ciganek, E. *Org. React. (N.Y.)*, **1984**, *32*, 1. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (c) Taber, D. F. *Intramolecular Diels−Alder and Alder Ene Reactions*; Springer-Verlag, Berlin, 1984. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (e) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Volume 2, p 91. (f) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990, Chapter 3. (g) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Volume 5, Chapter 4.4. (h) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464.

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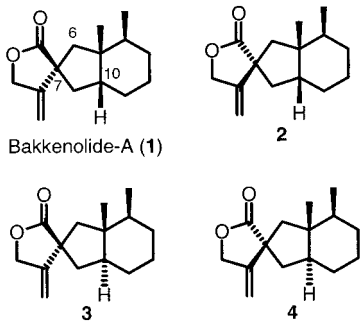
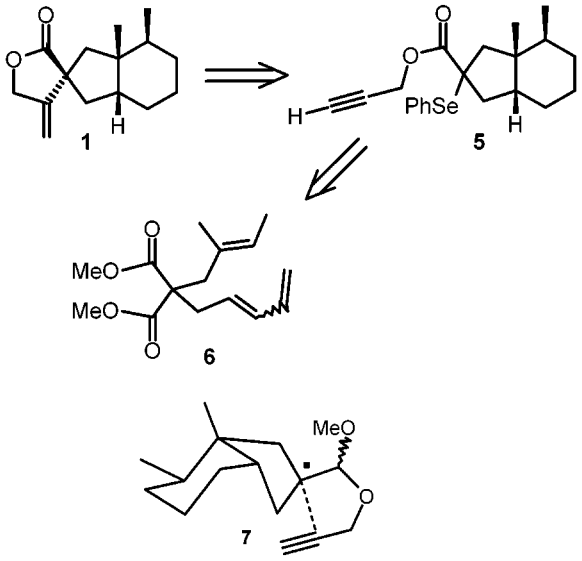


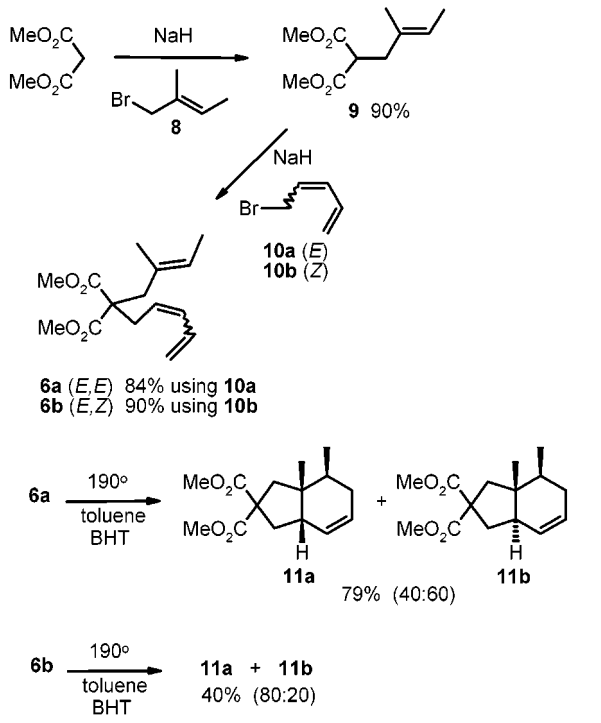
Scheme 1



Alder reaction is followed by a radical cyclization ensuing from the homolytic cleavage of the phenylseleno group in **5**. Our intention was to control the stereochemistry of the hydrindane ring system (i.e. *cis*- vs *trans*-fused) by appropriate choice of *E* or *Z* geometry of the diene moiety (vide infra) of **6**. Previous studies[11] of intramolecular Diels−Alder reactions of other 1,3,8-nonatrienes have revealed that compounds containing a (3*Z*)-diene moiety favor the formation of *cis*-hydrindanes, whereas the corresponding (3*E*)-dienes afford poorer stereoselectivity favoring the *trans*-fused cycloadducts. Moreover, a precedent for obtaining the desired configuration at the spiro center in the subsequent radical cyclization of **5** was found in the related *endo*-selective radical cyclization of acetal **7** during an earlier synthesis of **1** by Srikrishna et al.[6e]

Thus, dimethyl malonate was alkylated sequentially with tiglyl bromide **8**[12] to afford **9**, followed by either (*E*)- or (*Z*)-5-bromo-1,3-pentadiene (**10a** and **10b**, respectively; Scheme 2).[13] The products **6a** and **6b** were then subjected to the intramolecular Diels−Alder reaction in toluene in a sealed Parr apparatus at 190 °C. Improved yields were

Scheme 2



obtained when a small amount of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT) was included in the reaction mixture to suppress polymerization, which was probably initiated by traces of peroxides in the absence of BHT. The *E*,*E*-triene **6a** thus produced a high yield of the unseparated mixture of *cis*- and *trans*-fused cycloadducts **11a** and **11b**, respectively, in the ratio of 40:60, as determined by NMR integration. As expected, a much improved ratio of 80:20 in favor of the desired *cis*-fused product **11a** was produced similarly from the *E*,*Z*-isomer **6b**, albeit in considerably lower yield (Scheme 2).

The product **11a**,**b** was hydrogenated to afford **12a**,**b** quantitatively. The mixture of *cis*- and *trans*-fused hydrindanes (series **a** and **b**, respectively, in Scheme 3) was then carried through subsequent steps because of difficulties in separating the two isomers. Identification of the *cis* and *trans* isomers in the mixtures of products was possible by comparison of their NMR spectra with those of the final products **1**−**4** (vide infra). The mixture of diesters **12a**,**b** was subjected to saponification and decarboxylation, followed by esterification with propargyl or allyl alcohol to furnish esters **14a**,**b** and **15a**,**b**, and selenenylation to give **16a**,**b** and **17a**,**b**, respectively (Scheme 3). Finally, homolytic cleavage of the selenide[14] moiety of propargyl ester **16a**,**b** with tri-*n*-butyltin hydride was studied under a variety of conditions, including the slow addition of the tin hydride/AIBN mixture to **16a**,**b**. However, instead of the desired 5-exo-dig cyclization,[15] only reductive deselenization was observed, thereby regenerating **14a**,**b**. Similar results were obtained with triphenyltin hydride, while attempts to induce photolytic

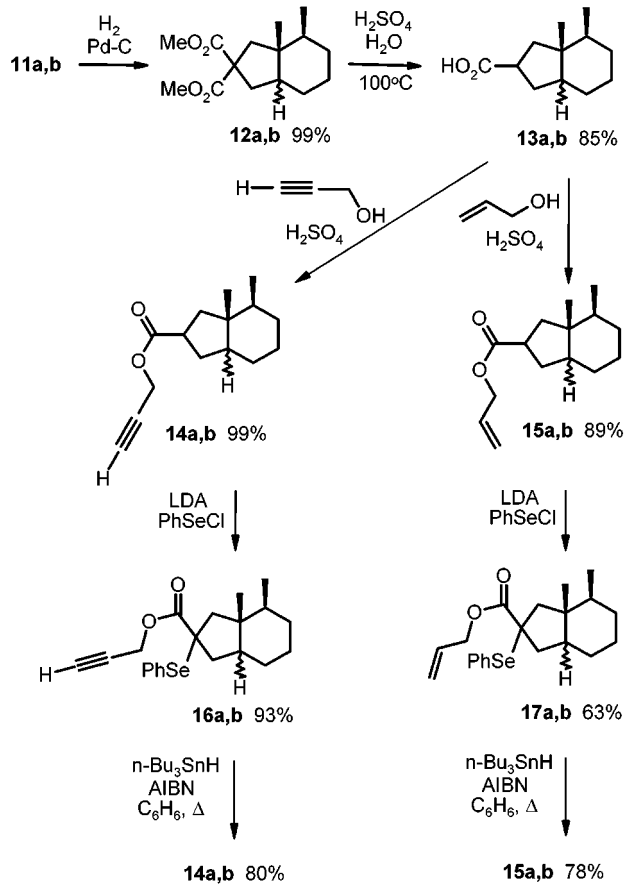
(11) (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960. (c) Boeckman, Jr., R. K.; Alessi, T. R. *J. Am. Chem. Soc.* **1982**, *104*, 3216.

(12) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925.

(13) The preparation of (*E*)-**10a** was achieved by a literature procedure: (a) Prévost, C.; Miginiac, P.; Miginiac-Groizeleau, L. *Bull. Soc. Chim. Fr.* **1964**, 2485. (*Z*)-**10b** was prepared by bromination of (*Z*)-2,4-pentadiene-1-ol with phosphorus tribromide. The (*Z*)-dienol was in turn obtained via the method of (b) Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411.

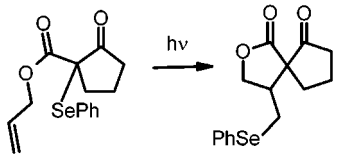
(14) (a) For homolytic cleavage of selenides with tin hydrides, see: Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438. (b) For a review of radical reactions and deselenizations of selenium compounds, see: Back, T. G. In *Organoselenium Chemistry − A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; Chapter 9.

Scheme 3

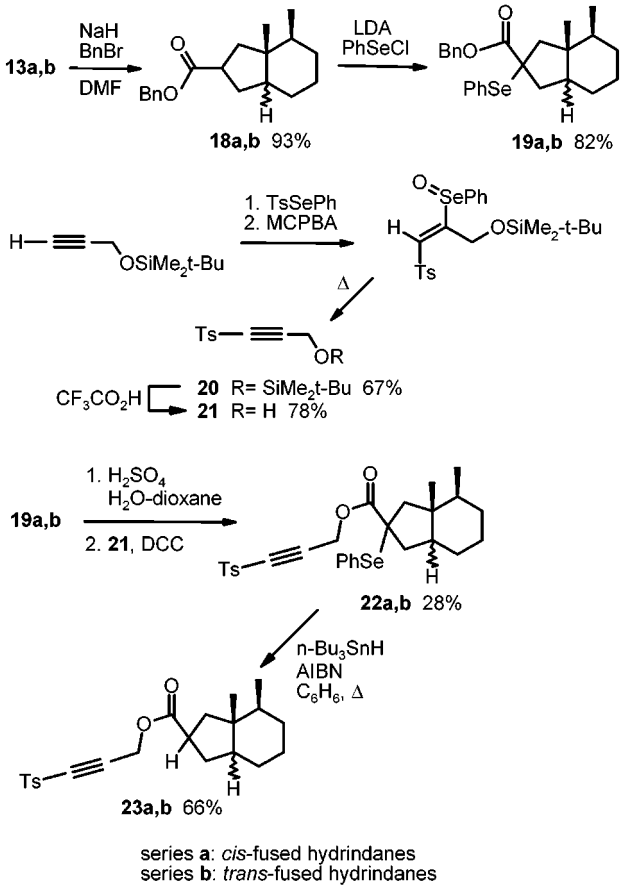


selenide cleavage and cyclization of **16a**,**b** also failed. The allyl ester **17a**,**b** was subjected to similar treatment, but again afforded only the products of reductive deselenization **15a**,**b**. The failure of radicals derived from **16a**,**b** or **17a**,**b** to cyclize, in contrast to the facile cyclization of **7**, is attributed to a more strained transition state when the acetylenic or allenic moiety is attached via an ester linkage instead of the acetal in **7**.[6e,16] This in turn permits hydrogen atom transfer from the tin hydride to the radical center to compete effectively with cyclization. However, it is also interesting to note that we,[8,17a] and later Byers et al.,[17b] observed that the radicals generated in the α-position of allyl and propargyl esters of *β*-keto cyclopentanecarboxylic acids cyclize smoothly to produce the corresponding spiro lactones (e.g., Scheme 4). Thus,

Scheme 4



Scheme 5



the failure of radicals derived from **16a**,**b** and **17a**,**b** to cyclize in an analogous manner was unexpected and remains somewhat puzzling.

The analogous radical cyclization step using a pendant acetylenic sulfone moiety was also investigated.[18] Selenenylation of the corresponding 3-(*p*-toluenesulfonyl)-propargyl ester analogue of **14a**,**b** was unsuccessful. Therefore, the selenenylation step was carried out first, using the benzyl ester **18a**,**b**, followed by saponification and reesterification with alcohol **21**. The latter compound was in turn prepared from the selenosulfonation, selenoxide elimination, and deprotection of propargyl *tert*-butyldimethylsilyl ether[19] (Scheme 5). Again, treatment of ester **22a**,**b** with tri-*n*-butyltin hydride and AIBN afforded only the product of reductive deselenization **23a**,**b**. Attempts were also made to effect an intramolecular conjugate addition of the ester enolate of **23a**,**b**

(15) For reviews of radical cyclization, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986; Chapter 4. (b) Curran, D. P. *Synthesis* **1988**, 417. (c) Curran, D. P. *Synthesis* **1988**, 489. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (e) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.2. (f) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992, Chapter 7. (g) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (h) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (i) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996. (j) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

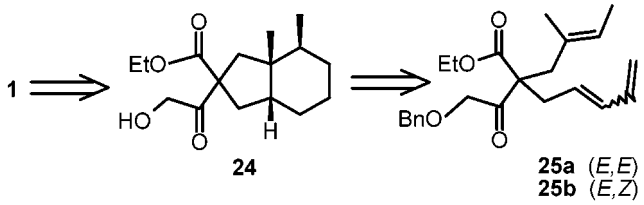
(16) Nevertheless, other types of spiro-*γ*-lactones have been prepared by 5-exo-dig cyclizations of radicals derived from propargyl α-bromoacetates; see: Kolt, R. J.; Griller, D.; Wayner, D. D. M. *Tetrahedron Lett.* **1990**, *31*, 7539.

(17) (a) Back, T. G.; Gladstone, P. L. *Synlett* **1993**, 699. (b) Byers, J. H.; Shaughnessy, E. A.; Mackie, T. N. *Heterocycles* **1998**, *48*, 2071.

(18) (a) For another example of a 5-exo-dig radical cyclization of an acetylenic sulfone, see: Bogen, S.; Gulea, M.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1999**, 64, 4920. (b) For a review of acetylenic and allenic sulfones, see: Back, T. G. *Tetrahedron* **2001**, in press.

(19) The selenosulfonation of the *tert*-butyldimethylsilyl ether of propargyl alcohol and oxidation to the corresponding selenoxide was carried out as reported previously: Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1987**, *52*, 4265.

Scheme 6



to the acetylenic sulfone moiety.[20] However, in all cases, only complex mixtures were produced.

To circumvent the unsuccessful radical cyclization step, we next attempted to produce the spiro lactone moiety by lactonization of **24**, in turn obtained by the intramolecular Diels−Alder reaction of **25**, followed by a Wittig reaction to install the exocyclic double bond, as shown retrosynthetically in Scheme 6. The known[21] β-keto ester **26** was thus alkylated with tiglyl bromide (**8**) and, separately, with dienyl bromides **10a** or **10b** to produce the pre-Diels−Alder trienes **25a** and **25b**, respectively. The intramolecular Diels−Alder reaction of each triene was carried out separately, as in the case of **6a** and **6b**, to afford the cycloadduct **28** as a mixture of four possible diastereomers (Scheme 7), which again could not be separated at this stage. The unseparated mixture derived from each of **25a** and **25b** (series **a** and **b**, respectively, in subsequent steps in Scheme 7) was therefore subjected to simultaneous hydrogenation and hydrogenolysis of the benzyl group, followed by spontaneous or acid-catalyzed lactonization, and a Wittig reaction. When the *E*,*E*-isomer **25a** was used, a high yield of 95% of cycloadduct **28a** was obtained, which afforded 90% of lactone **29a** and, following the Wittig step, 62% of a mixture of (±)-bakkenolide-A (**1**) and its 7-epi-, 10-epi-, and 7,10-diepi analogues (**2**−**4**, respectively) in the ratio of 24:10:34:32, in which the *trans*-fused (10-epi) isomers **3** and **4** dominated. A lower yield of 54% was produced in the cycloaddition of the *E*,*Z*-isomer **25b**, but the remaining steps were comparable in yield to those from **25a**. However, the final product mixture contained **1**−**4** in the very different ratio of 54:19:16:11, thus strongly favoring the *cis*-fused isomers **1** and **2**.

Products **1**−**4** were separated by preparative reverse phase HPLC. Bakkenolide-A (**1**) was identified by comparison to an authentic sample (GC-MS, ^{1}H and ^{13}C NMR), while its epi-spiro stereoisomer **2** had spectroscopic properties consistent with those reported in the literature.[7k] Stereoisomers **3** and **4**, which both contain *trans*-fused hydrindanes and differ from each other in the relative configurations of their spiro centers, are new compounds that were fully characterized. It was possible to distinguish them on the basis of an NOE that was observed between the angular methyl group and one of the exocyclic methylene protons in one epimer (assigned structure **4**), while the other epimer (assigned structure **3**) showed no such effect. Moreover, a small long-range coupling of ca. 0.8 Hz was observed between the angular methyl group and the proton at C-10 in the *trans*-fused diastereomers **3** and **4**, as well as in several of their synthetic precursors. No such coupling was discerned in the *cis*-fused series.

(20) For a review of conjugate additions to acetylenic sulfones, see: ref 18b and Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993; Chapter 4.

(21) Meul, T.; Miller, R.; Tenud, L. *Chimia* **1987**, *41*, 73.

The stereochemistry of the intramolecular Diels−Alder reaction requires further comment. Four transition states A−D (Scheme 8) are possible (neglecting stereochemistry associated with the spiro center), depending on whether the geometry of the pre-Diels−Alder triene moiety is *E*,*E* or *E*,*Z*, and on whether an exo or endo approach is taken between the diene and dienophile components. Extensive earlier investigations of intramolecular Diels−Alder reactions[10] have shown that the partitioning between exo and endo transition states depends on the length and nature of the tether, the *E*,*Z* configurations of the triene, and the nature and location of substituents and activating groups. In (3*E*)-1,3,8-nonatrienes, the corresponding exo and endo transition states are often comparable, resulting in poor stereoselectivity, generally favoring the *trans*-hydrindane.[11] On the other hand, the endo transition state of (3*Z*)-nonatrienes is significantly more strained than the exo, thus leading to higher stereoselectivity in favor of the corresponding *cis*-hydrindane.[11] In the present case, as expected, *cis*-fused cycloadducts were formed preferentially (*cis*:*trans* = 80:20 and 73:27) from *E*,*Z*-**6b** and *E*,*Z*-**25b**, respectively, indicating that transition state A (exo) is favored over C (endo). Similarly, exo transition state D was slightly preferred over endo-B when the isomeric *E*,*E*-**6a** and *E*,*E*-**25a** were employed, resulting in the selective formation of the corresponding *trans*-fused cycloadducts, but with relatively poor stereoselectivity (*cis*:*trans* = 40:60 and 34:66, respectively). However, the reason for the preferential formation of the bakkenolide-A spiro-configuration (i.e., in **1** and **3**), as opposed to the 7-epi configuration (in **2** and **4**), is less clear.

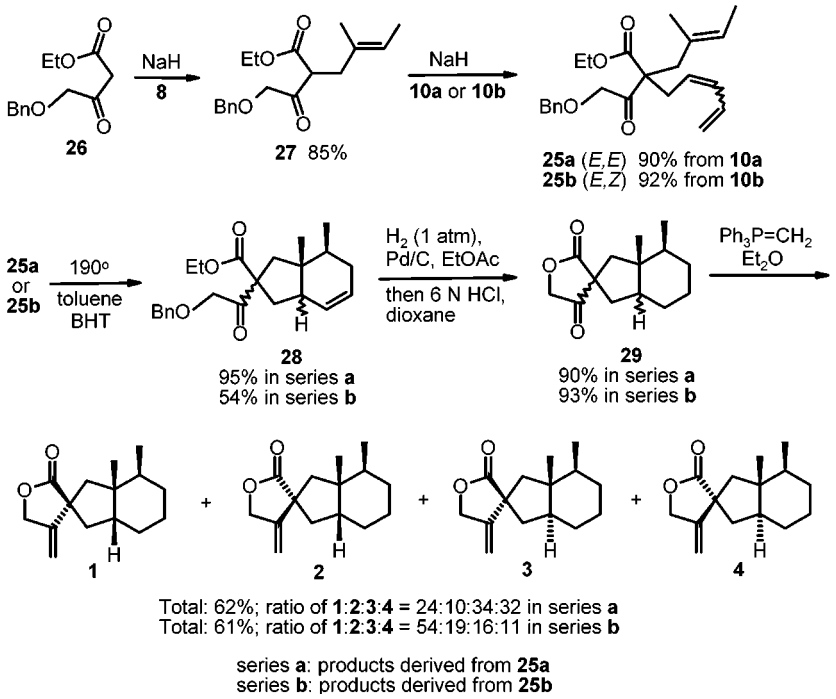
The method in Scheme 7 therefore provides a simple five-step synthetic approach from keto ester **26** to (±)-bakkenolide-A (**1**), which was formed stereoselectively when the *E*,*Z*-triene **25b** was employed in the key intramolecular Diels−Alder step. Minor amounts of the 7-epi- 10-epi-, and 7,10-diepibakkenolide-A stereoisomers **2**−**4** were also isolated. Thus, the *E*,*Z*-isomer **25b** underwent preferential exo cycloaddition, leading to *cis*-fused hydrindane products **1** and **2**. On the other hand, exo cycloaddition of the corresponding *E*,*E*-triene **25a** resulted in the stereoselective formation of *trans*-fused hydrindane cycloadducts, thus favoring the novel 10-epi- and 7,10-diepibakkenolide-A stereoisomers **3** and **4**. Since the opportunity exists to introduce further modifications to the diene and dienophile components before their incorporation into the β-keto ester **26**, this approach may also provide general access to other, more highly substituted members of the bakkenolide family.

Experimental Section

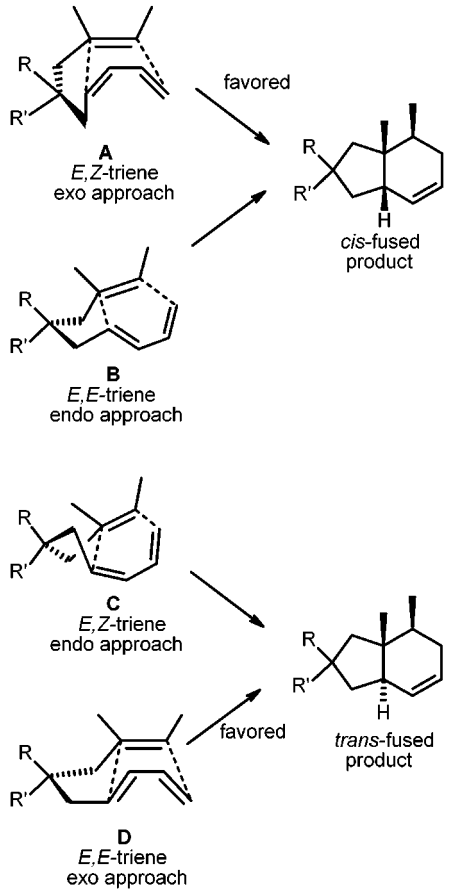
NMR spectra were recorded in deuteriochloroform and are reported relative to residual chloroform or TMS as the internal standard. Mass spectra were obtained by EI at 70 eV. Chromatography refers to flash chromatography on silica gel (230−400 mesh), unless otherwise noted.

Dimethyl 2-[2-Methyl-2(*E*)-butenyl]malonate (9). Dimethyl malonate (3.5 g, 27 mmol) in 10 mL of THF was added dropwise to NaH (700 mg, 29 mmol) in 250 mL of dry THF, and the mixture was stirred for 30 min at room temperature. A solution of tiglyl bromide[12] (4.0 g, 27 mmol) in 10 mL of THF was then added dropwise. After 18 h, the reaction was quenched with 100 mL of saturated aqueous NH_4Cl solution. The aqueous phase was separated and extracted with ether (3 × 100 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was

Scheme 7



Scheme 8



chromatographed (hexanes:ethyl acetate, 5:1) to afford 4.8 g (90%) of **9** as a colorless oil; IR (neat): 1738, 1337, 1236, 1152 cm^{-1}; ^1H NMR (400 MHz): δ 5.28 (q, J = 6.6 Hz, 1H), 3.72 (s, 6 H), 3.58 (t, J = 7.8 Hz, 1 H), 2.59 (d, J = 7.8 Hz, 2 H), 1.62 (s, 3 H), 1.56 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.0, 131.8, 122.0, 52.8, 51.0, 39.0, 15.7, 13.8; MS (*m*/*z*, %) 200 (41, M^+), 81 (100).

(*Z*)-5-Bromo-1,3-pentadiene (10b). A mixture of (*Z*)-2,4-pentadien-1-ol (0.900 g, 10.7 mmol) and PBr_3 (0.42 mL, 4.4 mmol) in 10 mL of ether was stirred for 2 h at 0 °C in a flask wrapped in aluminum foil. Ice−water (10 mL) was added to quench the reaction, and the mixture was extracted with ether (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was carefully removed under reduced pressure at room temperature. The product, which is a strong lachrymator, was distilled, bp 42−43 °C (25 mmHg), to afford 1.15 g (72%) of **10b** as a colorless liquid; ^1H NMR δ 6.69 (dt, J = 16.8, 10.7 Hz, 1 H), 6.14 (t, J = 10.8 Hz, 1 H), 5.73 (m, 1 H), 5.43−5.26 (m, 2 H), 4.13 (d, J = 8.5 Hz, 2 H). The NMR spectrum compares favorably with the signals attributed to the *Z*-component of an *E*,*Z*-mixture of **10** reported in the literature.[22]

Dimethyl 2-[2-Methyl-2(*E*)-butenyl]-2-[2(*E*)-4-pentadienyl]malonate (6a). Diester **9** (2.86 g, 14.3 mmol) in 5 mL of THF was added dropwise to NaH (377 mg, 15.7 mmol) in 75 mL of dry THF, and the mixture was stirred for 30 min at room temperature. A solution of (*E*)-5-bromo-1,3-pentadiene **10a**[13a] (2.10 g, 14.3 mmol) in 3 mL of THF was then added dropwise. After 18 h, the reaction was quenched with 50 mL of saturated aqueous NH_4Cl solution. The aqueous phase was separated and extracted with ether (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (hexane: ethyl acetate, 10:1) to afford 3.2 g (84%) of (*E*,*E*)-**6a** as a colorless oil; IR (neat): 1736, 1203, 1007 cm^{-1}; ^1H NMR (400 MHz) δ 6.28 (dt, J = 10.3, 16.9 Hz, 1 H), 6.06 (dd, J = 10.4, 15.1 Hz, 1 H), 5.55 (dt, J = 7.6, 15.1 Hz, 1 H), 5.29 (q, J = 6.7 Hz, 1 H), 5.11 (d, J = 16.9 Hz, 1 H), 5.01 (d, J = 10.1 Hz, 1 H), 3.70 (s, 6 H), 2.67 (s, 2 H), 2.64 (d, J = 7.7 Hz, 2 H), 1.57 (d, J = 6.7 Hz, 3 H), 1.52 (s, 3 H); ^{13}C NMR (100 MHz) δ 172.1, 137.1, 135.1, 130.8, 128.8, 125.1, 116.6, 58.3, 52.6, 43.0, 36.3, 16.8, 14.0; MS (*m*/*z*, %) 266 (0.18, M^+), 165 (82), 41 (100). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.50.

Dimethyl 2-[2-Methyl-2(*E*)-butenyl]-2-[2(*Z*)-4-pentadienyl]malonate (6b). The procedure for preparing **6a** was repeated with NaH (142 mg, 5.9 mmol), diester **9** (984 mg, 4.9 mmol), and (*Z*)-5-bromo-1,3-pentadiene (723 mg, 4.9 mmol) to

(22) Dienyl bromide**10** has also been prepared as an *E*,*Z*-mixture: Davies, A. G.; Griller, D.; Ingold, K. U.; Lindsay, D. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 633.

afford 1.17 g (90%) of **6b** as a colorless oil; IR 1736, 1286, 1201, 1101 cm^{-1}; ^1H NMR (400 MHz) δ 6.60 (ddt, J = 16.8, 10.6, 1.0 Hz, 1 H), 6.09 (t, J = 11.0 Hz, 1 H), 5.36−5.24 (m, 2 H), 5.20 (dd, J = 16.8, 1.7 Hz, 1 H), 5.13 (d, J = 10.1 Hz, 1 H), 3.69 (s, 6 H), 2.77 (dd, J = 7.8, 1.5 Hz, 2 H), 2.68 (s, 2 H), 1.56 (dd, J = 6.7, 0.8 Hz, 3 H), 1.51 (s, 3 H); ^{13}C NMR (100 MHz) δ 171.7, 132.4, 131.8, 130.2, 125.5, 124.8, 118.2, 57.5, 52.3, 42.4, 30.5, 16.3, 13.6; MS (*m*/*z*, %) 266 (0.2, M^+), 165 (85), 41(100). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.46; H, 8.22.

Intramolecular Diels−Alder Cycloaddition of (*E*,*E*)-Triene 6a and (*E*,*Z*)-Triene 6b. Triene **6a** (2.00 g, 7.52 mmol), BHT (200 mg), and 400 mL of toluene were heated at 190 °C for 24 h in a sealed Parr apparatus. The toluene was removed under reduced pressure, and the residue was chromatographed (hexanes:ethyl acetate, 10:1) to afford 1.58 g (79%) of an unseparated mixture of *cis- and trans*-hydrindanes **11a** and **11b**, respectively, as a pale yellow oil in the ratio of 40:60, as determined by NMR integration; IR (neat) 1734, 1250, 1194, 1165 cm^{-1}; ^1H NMR (400 MHz) δ 5.65−5.50 (m, 2 H, both isomers), 3.73 (s, 3 H, both isomers); 3.70 (s, 3 H, **11b**), 3.69 (s, 3 H, **11a**), 2.69−1.45 (m, 8 H, both isomers), 0.90 (d, J = 6.7 Hz, 3 H, **11a**), 0.88 (d, J = 6.6 Hz, 3 H, **11b**), 0.87 (s, 3 H, **11a**), 0.59 (d, J = 0.8 Hz, 3 H, **11b**); MS (*m*/*z*, %) 266 (3, M^+), 147 (100). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.27; H, 8.59.

The reaction was repeated with the (*E*,*Z*)-triene **6b** as in the case of **6a** to afford 40% of an 80:20 mixture of hydrindanes **11a** and **11b**.

Diesters 12a,b. The 40:60 mixture of **11a**,**b** (1.58 g, 5.94 mmol) in 80 mL of ethyl acetate containing 50 mg of 10% Pd/C was stirred under hydrogen at 1 atm of pressure and room temperature for 24 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was chromatographed (hexanes:ethyl acetate, 10:1) to yield 1.57 g (99%) of an unseparated mixture of *cis*- and *trans*-hydrindane isomers **12a** and **12b**, obtained in the same 40:60 ratio (NMR integration) as a colorless oil; IR (neat) 1734, 1255, 1192, 1096 cm^{-1}; ^1H NMR (400 MHz) δ 3.73 (s, 6 H, **12b**); 3.72 (s, 3 H, **12a**), 3.71 (s, 3 H, **12a**), 2.60−1.00 (m, 12 H, both isomers), 0.91 (s, 3 H, **12a**), 0.84 (d, J = 6.6 Hz, 3 H, **12b**), 0.80 (d, J = 6.6 Hz, 3 H, **12a**), 0.62 (d, J = 0.7 Hz, 3 H, **12b**); MS (*m*/*z*, %) 268 (<0.1, M^+), 145 (100). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.76; H, 8.86.

Carboxylic Acids 13a,b. The 40:60 mixture of diesters **12a**,**b** (1.57 g, 5.86 mmol) was refluxed in 150 mL of 15% aqueous H_2SO_4 for 4 days. The reaction mixture was then basified with NaOH to pH 14 and extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to afford 161 mg (10%) of recovered **12a**,**b**. The aqueous phase was acidified to pH 2 and placed in a continuous extraction apparatus with ether for 24 h. The organic extract was dried over $MgSO_4$ and evaporated to provide 981 mg (85%) of a 40:60 mixture of *cis* and *trans* isomers **13a** and **13b**, each obtained as a pair of stereoisomers,[23] in the form of a colorless oil; IR (neat) 3200−2500, 1702, 1231, 942 cm^{-1}; ^1H NMR (400 MHz) δ 13.0 (broad s, 1 H, all isomers), 2.90 (m, 1 H, all isomers), 2.20−1.10 (m, 12 H, all isomers), 0.91 (s, 3 H, **13a**, minor isomer), 0.89 (s, 3 H, **13a**, major isomer), 0.84, 0.83, 0.80 and 0.79 (four overlapping d, each with J = 6.6 Hz, 3 H, all isomers), 0.64 (d, J = 0.9 Hz, 3 H, **13b**, major isomer), 0.62 (d, J = 0.9 Hz, 3 H, **13b**, minor isomer); MS (*m*/*z*, %) 196 (22, M^+), 109 (82), 40 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.16; H, 10.42.

Propargyl esters 14a,b. The mixture of isomers of **13a**,**b** (300 mg, 1.53 mmol) and propargyl alcohol (428 mg, 7.65 mmol) was refluxed in 30 mL of chloroform containing several drops of concentrated H_2SO_4 for 5 h. The mixture was washed with water and saturated aqueous Na_2CO_3 solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (hexane:ethyl acetate, 10:1) to afford 355 mg (99%) of a 40:60 mixture of *cis* and *trans* isomers **14a** and **14b**, each obtained as a pair of stereoisomers, as a colorless oil; IR (neat): 3303, 2126, 1736, 1163 cm^{-1}; ^1H NMR (400 MHz) δ 4.66−4.65 (four s, 3 H, all isomers), 2.90 (m, 1 H, all isomers), 2.45−2.43 (four s, 1 H, all isomers), 2.20−0.90 (m, 12 H, all isomers), 0.89 (s, 3 H, **14a**, minor isomer), 0.87 (s, 3 H, **14a**, major isomer), 0.83, 0.82, 0.78, 0.77 (four overlapping d, each with J = 6.7 Hz, 3 H, all isomers), 0.62 (d, J = 0.9 Hz, 3 H, **14b**, major isomer), 0.60 (d, J = 0.9 Hz, 3 H, **14b**, minor isomer); MS (*m*/*z*, %) 234 (13, M^+), 179 (38), 124 (100). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.93; H, 9.36.

Allyl Esters 15a,b. The preparation of **15a**,**b** from 252 mg (1.28 mmol) of **13a**,**b** and 373 mg (6.43 mmol) of allyl alcohol was carried out in 89% yield by the same procedure as used in the preparation of **14a**,**b**. The product was obtained as a 40:60 mixture of *cis* and *trans* isomers **15a** and **15b**, each formed as a pair of stereoisomers, in the form of a colorless oil; IR (neat) 1731, 1163, 983, 922 cm^{-1}; ^1H NMR (400 MHz) δ 5.91 (m, 1 H, all isomers), 5.29 (crude d, J = 17.2 Hz, 1 H, all isomers), 5.20 (crude d, J = 10.4 Hz, 1 H, all isomers), 4.55 (m, 2 H, all isomers), 2.85 (m, 1 H, all isomers), 2.10−1.00 (m, 12 H, all isomers), 0.89 (s, 3 H, **14a**, minor isomer), 0.87 (s, 3 H, **14a**, major isomer), 0.83, 0.82, 0.78, 0.77 (four overlapping d, each with J = 6.7 Hz, 3 H, all isomers), 0.62 (d, J = 0.7 Hz, 3 H, **14b**, major isomer), 0.60 (d, J = 0.7 Hz, 3 H, **14b**, minor isomer); MS (*m*/*z*, %) 236 (42, M^+), 179 (83), 149 (100). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.25; H, 9.93.

α-Phenylseleno Propargyl Esters 16a,b. A solution of LDA (0.32 mmol) in 5 mL of dry THF was cooled to −78 °C, and the mixture of isomers **14a**,**b** (50 mg, 0.21 mmol) in 1 mL of THF was added dropwise via syringe. After 15 min, this was followed by the similar addition of benzeneselenenyl chloride (40 mg, 0.21 mmol) in 1 mL of THF. The solution was stirred at −78 °C for 1 h and then warmed slowly to room temperature and quenched with 10 mL of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (hexanes:ethyl acetate, 10:1) to afford 77 mg (93%) of **16a**,**b** as a mixture of stereoisomers in the form of a yellow oil; IR (neat) 2182, 1726, 1243, 1173, 737 cm^{-1}; ^1H NMR (400 MHz) δ (signals from individual stereoisomers could not be identified) 7.65−7.20 (m, 5 H), 5.00−4.50 (m, 2 H), 2.70−1.00 (m, 13 H), 1.00−0.50 (m, 6 H). Anal. Calcd for $C_{21}H_{26}O_2Se$: C, 64.78; H, 6.73. Found: C, 64.41; H, 6.91.

α-Phenylseleno Allyl Esters 17a,b. The preparation of **17a**,**b** from 200 mg (0.85 mmol) of **15a**,**b** was carried out in 63% yield by the same procedure used in the preparation of **16a**,**b**. The product **17a**,**b** was obtained as a mixture of stereoisomers in the form of a yellow oil; IR (neat) 1716, 1239, 1168 cm^{-1}; ^1H NMR (400 MHz) (signals from individual stereoisomers could not be identified) δ 7.65−7.15 (m, 5 H), 6.00−5.73 (m, 1 H), 5.35−4.90 (m, 2 H), 4.65−4.40 (m, 2 H), 2.70−1.00 (m, 12 H), 1.00−0.50 (m, 6 H).

Reaction of Selenides 16a,b with Tri-*n*-butyltin Hydride. The mixture of stereoisomers of **16a**,**b** (30 mg, 0.08 mmol) was refluxed in 5 mL of dry, degassed benzene under an argon atmosphere. A solution of tri-*n*-butyltin hydride (33 mg, 0.11 mmol) and AIBN (5 mg, 0.03 mmol) in 5 mL of benzene was added over 3 h via a syringe pump. The solution was refluxed for another 3 h and then concentrated under reduced pressure. The residue was chromatographed (hexanes: ethyl acetate, 10:1) to afford 14.5 mg (80%) of **14a**,**b** as colorless oil, identical to an authentic sample.

Reaction of Selenides 17a,b with Tri-*n*-butyltin Hydride. The mixture of stereoisomers of **17a**,**b** (30 mg, 0.08 mmol) was treated with tri-*n*-butyltin hydride as in the preceding procedure to afford 14 mg (78%) of **15a**,**b** as colorless oil, identical to an authentic sample.

Benzyl Ester 18a,b. Carboxylic acid **13a**,**b** (70 mg, 0.36 mmol) and NaH (35 mg, 1.4 mmol) were stirred in 6 mL of dry DMF for 30 min. Benzyl bromide (244 mg, 1.43 mmol) in 1 mL of DMF was added dropwise, and the resulting solution

(23) The (2α,3a*β*,4*β*,7aα)-steroisomer of **13b** has been reported: Ferraz, H. M. C.; Silva, L. F., Jr. *J. Org. Chem.* **1998**, *63*, 1716.

was stirred for 12 h at room temperature. The solvent was evaporated under vacuum, and 10 mL of water and 20 mL of ether were added. The aqueous phase was extracted repeatedly with ether, and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The product was chromatographed (hexanes:ethyl acetate, 10:1) to afford 95 mg (93%) of a 40:60 mixture of *cis* and *trans* isomers **18a** and **18b**, each formed as a pair of stereoisomers, in the form of a colorless oil; IR (neat) 1731, 1156 cm^{-1}; ^1H NMR (400 MHz) δ 7.37−7.34 (m, 5 H, all isomers), 5.13−5.10 (m, 2 H, all isomers), 2.92 (m, 1 H, all isomers), 2.30−1.00 (m, 12 H, all isomers), 0.89 (s, 3 H, **18a**, major isomer), 0.87 (s, 3 H, **18a**, minor isomer), 0.83, 0.82, 0.79, 0.75 (four overlapping d, each with J = 6.6 Hz, 3 H, all isomers), 0.62 (d, J = 0.7 Hz, 3 H, **18b**, minor isomer), 0.61 (d, J = 0.7 Hz, 3 H, **18b**, major isomer); MS (*m*/*z*, %) 286 (18, M^+), 179 (14), 149 (62), 91 (100). HRMS calcd for $C_{19}H_{26}O_2$: 286.1933; Found: 286.1944.

α-Phenylseleno Benzyl Esters 19a,b. The mixture of stereoisomers of **18a**,**b** (95 mg, 0.33 mmol) was selenenylated by the same procedure used in the preparation of **16a**,**b** to afford 120 mg (82%) of **19a**,**b** as a mixture of stereoisoimers in the form of a yellow oil; IR (neat) 1721, 1250, 1178 cm^{-1}; ^1H NMR (400 MHz) (signals from individual stereoisomers could not be identified) δ 7.55−7.20 (m, 5 H), 5.21−4.90 (m, 2 H), 2.70−1.00 (m, 12 H), 1.00−0.50 (m, 6 H); MS (*m*/*z*, %) 442 (2, M^+), 193 (55), 149 (78, 91 (100). HRMS calcd for $C_{25}H_{30}O_2$-Se: 442.1411; Found: 442.1426.

3-(*p*-Toluenesulfonyl)-2-propyn-1-ol (21) and its *tert*-Butyldimethylsilyl Ether 20. (*E*)-1-(*tert*-Butyldimethylsilyloxy)-2-(phenylseleno)-3-(*p*-toluenesulfonyl)-2-propen-1-ol and the corresponding selenoxide were prepared as described previously.[19] The selenoxide (5.99 g, 12.0 mmol) and 10 g of anhydrous $MgSO_4$ were refluxed for 4 h in 300 mL of benzene. The mixture was then filtered, concentrated under reduced pressure, and chromatographed (hexanes:ethyl acetate, 9:1) to afford the corresponding acetylenic sulfone as an oil that crystallized from pentane to afford 2.61 g (67%) of the acetylenic sulfone **20** as white needles, mp 44−45 °C; IR (KBr) 2202, 1596, 1335, 1161 cm^{-1}; ^1H NMR (200 MHz) δ 7.89 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 4.42 (s, 2 H), 2.48 (s, 3 H), 0.85 (s, 9 H), 0.06 (s, 6 H); MS (*m*/*z*, %) 324 (1, M^+), 237 (75), 173 (79), 128 (100). Anal. Calcd. for $C_{16}H_{24}O_3SSi$: C, 59.22; H, 7.45. Found: C, 59.09; H, 7.30.

The above acetylenic sulfone **20** (1.00 g, 3.09 mmol) was stirred for 1 h in 20 mL of 50% aqueous trifluoroaceetic acid. The mixture was diluted with 30 mL of ethyl acetate, washed rapidly with 5% NaOH solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (hexanes:ethyl acetate, 3:1) to afford 0.507 g (78%) of **21** as a pale yellow oil that was best used without delay; ^1H NMR (200 MHz) δ 7.90 (d, J = 8.6 Hz, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 4.41 (s, 2 H), 2.48 (s, 3 H), 1.72 (br s, 1 H).

Acetylenic Sulfone 22a,b. The mixture of stereoisomers of α-phenylseleno benzyl ester **19a**,**b** (300 mg, 0.68 mmol) was refluxed in a mixture of 10 mL of 15% aqueous H_2SO_4 and 10 mL of 1,4-dioxane for 3 days. The reaction was basified with NaOH to pH 14 and washed with ether (3 × 20 mL). The combined organic layers afforded 126 mg of recovered **19a**,**b**. The aqueous phase was acidified to pH 2 and extracted with ether (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford 103 mg (43%) of the desired free α-phenylseleno carboxylic acid, contaminated with a small amount of the deselenized acid **13a**,**b**.

The partially purified α-phenylseleno carboxylic acid (60 mg, 0.17 mmol), acetylenic sulfone **21** (85 mg, 0.40 mmol) and DCC (140 mg, 0.68 mmol) were stirred in 10 mL of dry dichloromethane for 12 h at room temperature. The solvent was evaporated, and the residue was chromatographed (hexanes:ethyl acetate, 10:1) to afford 60 mg (64%) of **22a**,**b**, in the form of a yellow oil; IR (neat) 2212, 1700, 1342, 1229, 1163 cm^{-1}; ^1H NMR (400 MHz) (signals from individual stereoisomers could not be identified) δ 7.95−7.30 (m, 9 H), 4.90−4.55 (m, 2H), 2.43 (s, 3 H) superimposed on 2.70−1.10 (m, 12 H), 1.10−0.70 (m, 6 H). The product was used directly without further purification.

Reaction of Selenides 22a,b with Tri-*n*-butyltin Hydride. The mixture of stereoisomers of **22a**,**b** (30 mg, 0.055 mmol) was treated with tri-*n*-butyltin hydride as in the case of **16a**,**b** to afford 14 mg (66%) of a 40:60 mixture of *cis*- and *trans*-hydrindanes **23a** and **23b**, each consisting of nearly equal amounts of two stereoisomers (NMR integration), in the form of a light yellow oil; IR (neat) 2207, 1731, 1337, 1163, 1086 cm^{-1}; ^1H NMR (400 MHz) δ 7.87 (d, J = 8.3 Hz, 2 H), 7.37 (d, J = 7.9 Hz, 2 H), 4.76 (m, 2 H), 2.85 (m, 1 H), 2.46 (s, 3 H), 2.10−1.05 (m, 12 H), 0.88 (s, 3 H, one isomer of **23a**), 0.87 (s, 3 H, other isomer of **23a**), 0.83, 0.82, 0.78, 0.75 (four overlapping d, each with J = 6.6 Hz, 3 H, all isomers), 0.60 (d, J = 0.8 Hz, 3 H, one isomer of **23b**), 0.55 (d, J = 0.9 Hz, 3 H, other isomer of **23b**). Anal. Calcd for $C_{22}H_{28}O_4S$: C, 68.00; H, 7.26. Found: C, 67.75; H, 7.34.

Ethyl 4-Benzyloxy-2-[2-methyl-2(*E*)-butenyl]acetoacetate (27). A solution of β-keto ester **26** (10.3 g, 43.5 mmol) in 75 mL of THF was added dropwise over 10 min to NaH (60% suspension, 1.74 g, 43.5 mmol) in 100 mL of THF. After 30 min, tiglyl bromide (**8**) (6.48 g, 43.5 mmol) in 100 mL of THF was added dropwise over 15 min, and the reaction mixture was stirred for 18 h. It was then filtered and the THF was removed under reduced pressure. Water (150 mL) was added, and the mixture was extracted with ether (3 × 100 mL). The extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (hexanes:ethyl acetate, 1:5) afforded 11.2 g (85%) of **27** as a colorless oil; IR (neat) 1750, 1733 cm^{-1}; ^1H NMR (200 MHz) δ 7.35 (m, 5 H), 5.24 (m, 1 H), 4.58 (s, 2 H), 4.18−4.05 (m, 4 H), 3.82 (t, J = 7.6 Hz, 1 H), 2.55 (m, 2 H), 1.60 (t, J = 1.1 Hz, 3 H), 1.53 (crude d, J = 6.7 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H); MS (*m*/*z*, %) 258 (4), 207 (16), 167 (38), 91 (100). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.60; H, 8.20.

Ethyl 4-Benzyloxy-2-[2-methyl-2(*E*)-butenyl]-2-[2(*E*),4-pentadienyl]acetoacetate (25a). A solution of keto ester **27** (3.38 g, 11.1 mmol) in 10 mL of THF was added to NaH (60% suspension, 0.445 g, 11.1 mmol) in 25 mL of THF. The reaction mixture was stirred for 30 min, and a solution of bromide **10a** (1.65 g, 11.1 mmol) in 10 mL of THF was added. The reaction mixture was refluxed for 2 h and allowed to cool to room temperature. The mixture was filtered, and the THF was removed under reduced pressure. Water (75 mL) was added, and the mixture was extracted with ether (3 × 50 mL). The extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (hexanes:ethyl acetate, 7:1) afforded 3.69 g (90%) of **25a** as a colorless oil; IR (neat) 1745, 1718, 1609 cm^{-1};^1H NMR (200 MHz) δ 7.34 (m, 5 H), 6.25 (dt, J = 16.8, 10.2 Hz, 1 H), 6.10−5.93 (m, 1 H), 5.50 (dt, J = 14.7, 7.2 Hz, 1 H), 5.25 (m, 1 H), 5.14−4.97 (m, 2 H), 4.54 (s, 2 H), 4.19 (s, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 2.75−2.60 (m, 4 H), 1.63−1.47 (m, 6 H), 1.19 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ (50 MHz) 204.8, 171.4, 137.0, 136.6, 134.7, 130.6, 128.4, 128.3, 127.9, 127.7, 124.6, 116.3, 74.2, 73.3, 61.4, 61.0, 42.1, 35.5, 16.9, 14.0, 13.5; MS (*m*/*z*, %) 281 (27), 207 (100), 91 (93).

Ethyl 4-Benzyloxy-2-[2-methyl-2(*E*)-butenyl]-2-[2(*Z*)-4-pentadienyl]acetoacetate (25b). Product **25b** was prepared from 1.30 g (4.27 mmol) of keto ester **27**, 0.636 g (4.27 mmol) of *Z*-bromide **10b,** and NaH (60% suspension, 0.171 g, 4.28 mmol) via the same procedure as used for the preparation of **25a**. This afforded 1.45 g (92%) of **25b** as a colorless oil; ^1H NMR (200 MHz) δ 7.34 (m, 5 H), 6.58 (dt, J = 16.8, 10.6 Hz, 1 H), 6.08 (t, J = 11.1 Hz, 1 H), 5.35−5.06 (m, 4 H), 4.54 (s, 2 H), 4.18 (s, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.00−2.60 (m, 2 H), 2.69 (br s, 2 H), 1.57 (d, J = 4.4 Hz, 3 H), 1.50 (t, J = 1.2 Hz), 1.18 (t, J = 7.2 Hz, 3 H); MS (*m*/*z*, %) 281 (23), 207 (100), 91 (88). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.52; H, 8.50.

Intramolecular Diels−Alder Cycloaddition of (*E*,*E*)-Triene 25a and (*E*,*Z*)-Triene 25b. Compound **25a** (1.05 g, 2.84 mmol) in 400 mL of toluene containing BHT (200 mg) was heated at 190 °C for 24 h in a sealed Parr apparatus. The toluene was removed under reduced pressure, and chromatography of the residue (hexanes:ethyl acetate, 8:1) afforded 1.00 g (95%) of **28** as a mixture of stereoisomers in the form of a light yellow oil; IR (neat) 1746, 1715 cm^{-1}; ^1H NMR (400

MHz) (signals from individual stereoisomers could not be identified) δ 7.40−7.25 (m, 5 H), 5.70−5.55 (m, 2 H), 4.55 (m, 2 H), 4.25−4.00 (m, 4 H), 2.70−1.40 (m, 8 H), 1.21−1.14 (m, 3 H), 0.95−0.50 (m, 6 H); MS (*m*/*z*, %) 370 (M^+, 1), 279 (21), 233 (20), 147 (33), 91 (100). HRMS calcd for $C_{23}H_{30}O_4$: 370.2144. Found 370.2148.

The mixture of isomers of **28** was similarly prepared in 54% yield from compound **25b**.

Spiro Lactone 29. A mixture of isomers of **28** (57 mg, 0.15 mmol) obtained from **25a** and 20 mg of 10% Pd−C was stirred in 5 mL of ethyl acetate under 1 atm of hydrogen for 3 days. The mixture was then filtered through Celite, the filtrate was concentrated under reduced pressure, and the residue was chromatographed (hexanes:ethyl acetate, 5:1) to afford 39 mg (90%) of the corresponding hydroxy ester as a colorless oil that lactonized slowly and spontaneously upon standing. Alternatively, to accelerate lactonization, the hydroxy ester (81 mg, 0.30 mmol) was stirred for 7 h in 1.5 mL of dioxane and 0.5 mL of 6 M HCl. The mixture was then diluted with water and extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure, and chromatography of the residue (hexanes:ethyl acetate, 3:1) afforded 72 mg (quantitative) of a mixture of stereoisomers of **29** as a colorless oil; IR (neat) 1756, 1740 cm^{-1}; ^1H NMR (400 MHz) (signals from individual stereoisomers could not be identified) δ 4.72−4.56 (m, 2 H), 2.45−1.05 (m, 12 H), 1.00−0.80 (m, 6 H); MS (*m*/*z*, %) 236 (M^+, 5), 221 (6), 123 (100), 109 (77).

The mixture of isomers of **29** was similarly prepared in 93% yield from **28** that had been obtained from **25b**. The products were used directly without further purification.

Bakkenolide-A (1) and Its Stereoisomers 2−4. *n*-Butyllithum (2.17 M, 0.27 mL, 0.59 mmol) was added to methyltriphenylphosphonium iodide (0.24 g, 0.59 mmol) in 4 mL of dry ether. A solution of the mixture of stereoisomers of **29** (47.0 mg, 0.199 mmol; derived from *E*,*E*-triene **25a**) in 1 mL of ether was added, and the reaction mixture was stirred for an additional 2 h. The reaction was quenched with water, and the mixture was extracted with ether (5 × 10 mL). The combined extracts were dried over $MgSO_4$, the solvent was removed under reduced pressure, and chromatography of the residue (hexanes:ethyl acetate, 5:1) afforded 28.9 mg (62%) of the mixture of isomers **1**−**4** in the ratio of 24:10:34:32 (GC analysis). They were separated by preparative reversed phase HPLC (elution with methanol−water, 7:3) and eluted in the order: **1**, **2**, **4**, and **3**. Products **1**, **3**, and **4** were >95% pure, while **2** was obtained as a 4:1 mixture with **1**. The same products **1**−**4** were obtained in 61% yield in the ratio of 54:19:16:11 when the starting material **29** was obtained from *E*,*Z*-triene **25b**. The properties of the products are as follows.

(±)-Bakkenolide-A (**1**): ^1H NMR (400 MHz) δ 5.12 (m, 1 H), 5.04 (m, 1 H), 4.78 (m, 2 H), 2.26 (m, 1 H), 2.10 (t, J = 13.1 Hz, 1 H), 1.98 (m, 2 H), 1.70−1.40 (m, 7 H), 1.20 (m, 1 H), 1.00 (s, 3 H), 0.86 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 150.7, 106.0, 70.6, 50.1, 48.8, 46.4, 44.3, 42.6, 34.1, 31.1, 23.6, 21.2, 19.4, 16.6; MS (*m*/*z*, %) 234 (M^+, 10%), 219 (8), 124 (100), 123 (45), 111 (71). These spectra were identical to those obtained from an authentic sample provided by Dr. J. Harmatha of the Czech Academy of Sciences.

(±)-7-Epibakkenolide-A (**2**): ^1H NMR (200 MHz) δ 5.07 (m, 1 H), 4.99 (m, 1 H), 4.75 (m, 2 H), 2.47 (dd, J = 13.6, 12.3 Hz, 1 H), 2.41 (d, J = 14.2 Hz, 1 H), 2.10−1.40 (m, 10 H), 0.97 (s, 3 H), 0.82 (d, J = 6.6 Hz, 3 H); these signals were superimposed on those corresponding to **1**; the ratio of integrated intensities of signals of **2** to **1** was ca. 4:1; the NMR spectrum of **2** closely matches that reported in the literature;[7k] MS (*m*/*z*, %) 234 (M^+, 72%), 219 (30), 124 (78), 123 (82), 111 (100).

(±)-10-Epibakkenolide-A (**3**): ^1H NMR (400 MHz) δ 5.08 (m, 1 H), 4.97 (m, 1 H), 4.79 (m, 2 H), 2.17 (d, J = 13.2 Hz, 1 H), 2.06 (dd, J = 13.3, 12.2 Hz, 1 H), 1.80 (m, 2 H), 1.60−1.20 (m, 8 H), 0.91 (d, J = 0.8 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 151.9, 104.9, 70.1, 51.8, 50.2, 49.1, 45.4, 43.8, 42.3, 30.0, 26.4, 24.5, 17.2, 11.9; MS (*m*/*z*, %) 234 (M^+, 10%), 219 (7), 124 (67), 123 (100), 111 (80). HRMS calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1630.

(±)-7,10-Diepibakkenolide-A (**4**): ^1H NMR (400 MHz) δ 5.17 (m, 1 H), 5.03 (m, 1 H), 4.77 (m, 2 H), 2.09 (dd, J = 12.2, 5.8 Hz, 1 H), 1.99 (d, J = 12.8 Hz, 1 H), 1.90−1.13 (m, 10 H), 0.85 (d, J = 6.7 Hz, 3 H), 0.80 (d, J = 0.8 Hz, 3 H); double irradiation of the signal at δ 0.80 ppm resulted in an enhancement of 2% of the signal at δ 5.17 ppm; ^{13}C NMR (100 MHz) δ 149.9, 106.1, 70.5, 50.3, 49.3, 45.0, 43.1, 42.4, 30.0, 26.2, 24.5, 17.1, 13.1; MS (*m*/*z*, %) 234 (M^+, 5%), 219 (4), 124 (100), 123 (56), 111 (81). HRMS calcd for $C_{15}H_{22}O_2$, 234.1620: Found: 234.1627.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of both authentic and synthetic samples of **1**, ^1H NMR spectra of products **2**−**4**, and ^{13}C NMR spectra of new compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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