Synthesis of Terpenoid Unsaturated 1,4-Dialdehydes. π-Facial Selectivity in the Diels−Alder Reaction of the 1-Vinyl-2-methylcyclohexene Moiety of Polycyclic Systems with DMAD

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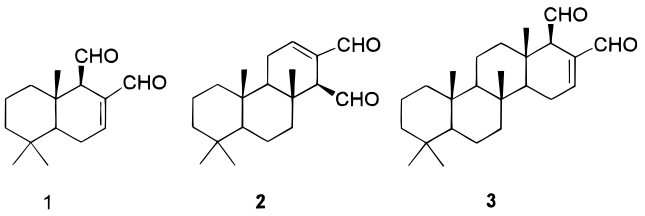
Introduction

An increasing number of polycyclic terpenoids containing the unsaturated 1,4-dialdehyde moiety, either as actual aldehyde groups or latent as γ-butenolide or furan rings, have been isolated from different terrestrial and marine sources.[1] The more representative compounds of this type show structures based on the drimane, spongiane, and scalarane skeletons (Scheme 1). Many of these compounds exhibit a variety of potent biological activities, including antibacterial, antifungal, antifeedant, antiinflammatory, antitumor-promoting, cytotoxic, enzyme-inhibiting, and plant growth regulatory properties,[1,2] that have greatly stimulated the synthetic work in this area of natural products.

Although a number of different synthetic approaches to natural products within this class have been reported,[3] the use of the intermolecular Diels−Alder reaction of an appropriately substituted 1,3-diene with dimethyl acetylenedicarboxylate (DMAD) to construct the B, C, or D ring of drimane, spongiane, and scalarane terpenoids, respectively, in a concise manner is particularly attractive (Scheme 2).

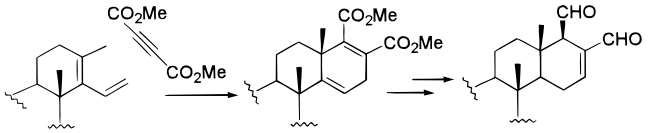
This strategy has been successfully used to prepare the simplest member of this group of natural products, polygodial (**1**), as well as many other drimane sesquiterpenes.[4] In connection with our synthetic studies on scalarane and spongiane terpenoids,[5] we have investigated the potential application of this Diels−Alder reaction to the synthesis of these polycyclic compounds. We report here the results of this study.

Scheme 1. Representative Terpenoid Unsaturated 1,4-dialdehydes with Drimane (1), Spongiane (2), and Scalarane (3) Skeletons

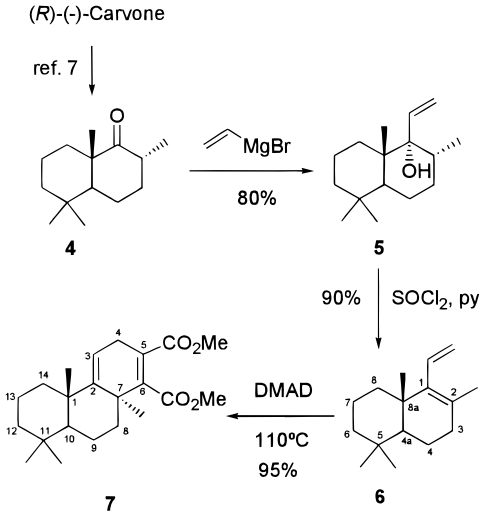


1 2 3

Scheme 2



Scheme 3



Results and Discussion

The Diels−Alder reaction of the diene **6** with DMAD as a potential route to the spongiane system was first studied. The synthesis of the diene **6**[6] is summarized in Scheme 3. The known decalone **4**, prepared in four steps from commercial (*R*)-(−)-carvone,[7] was treated with vinylmagnesium bromide in THF at low temperature to afford stereoselectively the axial alcohol **5** in 80% yield after chromatographic purification.[8] Finally, treatment of **5** with thionyl chloride−pyridine at low temperature cleanly furnished the diene **6**.

When a neat mixture of DMAD and the bicyclic diene **6** was heated at 110 °C for 24 h, a smooth and clean

(1) (a) Jonassohn, M.; Sterner, O. *Trends Org. Chem*. **1997**, *6*, 23 and references therein. (b) Connolly, J. D.; Hill, R. A. In *Dictionary of Terpenoids*, 1st ed.; Chapman and Hall: London, 1991; Vol. 1, p 453; Vol. 2, pp 895 and 1110. (c) Fraga, B. M. *Nat. Prod. Rep*. **1999**, *16*, 21 and previous reviews on sesquiterpenes of this series. (b) Hanson, J. R. *Nat. Prod. Rep*. **1999**, *16*, 209 and previous reviews on diterpenes of this series. (c) Faulkner, D. J. *Nat. Prod. Rep*. **1997**, *14*, 259 and previous reviews on sesterterpenes of this series.

(2) Jansen, B. J. M.; de Groot, A. *Nat. Prod. Rep*. **1991**, *8*, 309.

(3) (a) Jansen, B. J. M.; de Groot, A. *Nat. Prod. Rep*. **1991**, *8*, 319. (b) Zoretic, P. A.; Zhang, Y.; Fang, H. J.; Ribeiro, A.; Dubay, G. *J. Org. Chem*. **1998**, *63*, 1162. (c) Pattenden, G.; Roberts, L.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863 and references therein. (d) Corey, E. J.; Luo, G.; Lin, S. *J. Am. Chem. Soc*. **1997**, *119*, 9927 and references therein.

(4) For a review of the application of this strategy to the synthesis of drimane sesquiterpenes, see: (a) de Groot, A.; van Beek, T. A. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 1. See also: (b) Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579.

(5) (a) Abad, A.; Agulló, C.; Arnó, M.; Marin, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2193 and references therein. (b) Abad, A.; Agulló, C.; Cuñat, A. C.; Llosá, M. C. *J. Chem. Soc., Chem. Commun*. **1999**, 427.

(6) Racemic diene **6** has been previously prepared in nine synthetic steps from cyclohexane-1,3-dione: Daniewski, W. M.; Kubak, E.; Jurczak, J. *J. Org. Chem*. **1985**, *50*, 3963.

(7) Gesson, J. P.; Jacquesy, J. C.; Renoux, B. *Tetrahedron* **1989**, *45*, 5853.

(8) A 5−6% amount of the more polar epimeric equatorial alcohol was also obtained in this reaction (see Experimental Section). The equatorial disposition of the vinyl group in **5** was assigned by intramolecular NOE studies. In particular, irradiation of the vinylic

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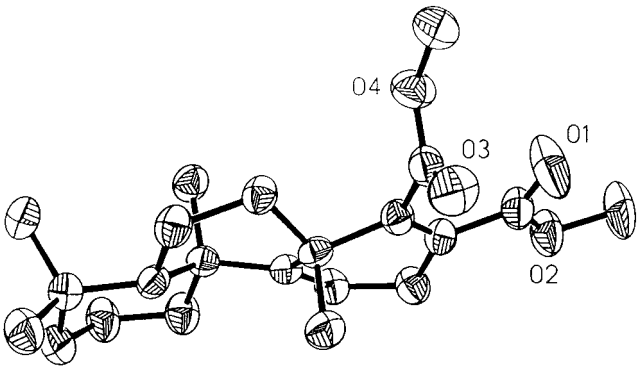


Figure 1. Molecular structure of **7** determined by X-ray crystallography.

reaction took place giving a chromatographically homogeneous approximately 95:5 mixture (^{1}H NMR analysis)[9] of Diels−Alder adducts in nearly quantitative yield. From this mixture, the major adduct could be obtained in analytically pure form by crystallization from hexane−dichloromethane. The structure **7** was initially assigned to this Diels−Alder adduct on the basis of intramolecular NOE studies and analysis of the ^{13}C NMR data. In particular, no NOE was observed upon irradiation of either the Me-7 (δ 1.31 ppm) or the Me-1 (δ 1.05 ppm) on each other, which strongly suggested the *anti* disposition of both methyl groups. Comparison of the chemical shift of the A/B rings carbon atoms with those of related epimeric compounds at C-7[10,11] revealed that C-10 (δ 43.98 ppm) is appreciably shifted upfield (between 8 and 9 ppm) in **7** with respect to those tricyclic compounds with a *syn* arrangement of the methyl groups at C-7 and C-1. This shielding of C-10 could not be explained by assuming a β orientation of the Me group at C-7 but should be in agreement with an α disposition of this group which forces the B ring to adopt a boatlike conformation.[10,12] This hypothesis was confirmed when suitable crystals for X-ray analysis could be obtained that unambiguously established the structure of **7** (Figure 1).

The formation of compound **7** as the major adduct in the Diels−Alder reaction of **6** with DMAD was unexpected and contrary to our initial assumption that the Diels−Alder condensation would take place by approach of the dienophile *anti* (below plane) to the angular methyl group at C-8a of the diene. It has been pointed out that steric effects are the main factor that control the face selectivity in Diels−Alder reaction of semicyclic dienes.[13] Examination of the lowest energy conformation of diene **6** suggests that, despite the slightly curved geometry adopted by the molecule to relieve the diaxial interaction between the methyl groups at C-8a and C-5, there does not seem to exist an evident steric bulk on the α-face that will direct the approach of the dienophile from the opposite face and much less to predict the high level of observed *syn*-selectivity. In fact, it has been previously observed that the Diels−Alder reaction of the same diene with a carbonyl heterodienophile[6] gave a 65:35 mixture of *anti* and *syn* Diels−Alder adducts, respectively. The same pattern has also been observed in the thermal cycloaddition reaction of a related diene (2-desmethyl) with 2,6-dimethylbenzoquinone,[10] in which the *anti*- and *syn*-adducts are obtained in a ratio that varies from 100:0 to 70:30 depending upon the reaction conditions used.

Theoretical calculations, using the GAUSSIAN98 program, have been carried out in order to understand the stereochemical outcome of the Diels−Alder reaction of **6** with DMAD. The geometry of the two transition structures, corresponding to the epimeric *syn*- and *anti*-adducts, was searched using the AM1 method, and it was not possible to find a concerted mechanism for the reaction. This could be due to the very well-known tendency of the semiempirical methods to give stepwise mechanisms in the Diels−Alder reactions. The transition structures were also optimized using low-level *ab initio* (HF/STO-3G) methods, due to the size of the system, and in this case two concerted and slightly asynchronous transition structures were found (see Figure 3 of the Supporting Information). However, the transition structure corresponding to the formation of the *anti*-adduct is favored by 0.9 kcal/mol, which is in contradiction with the facial selectivity experimentally observed. It is concluded from these preliminary calculations that semiempirical methods are not adequate to study this reaction and, if it takes place through a concerted mechanism, the theoretical study should be carried out using a high-level *ab initio* method.[14]

To determine if the observed selectivity in the above Diels−Alder reaction was related with the acetylenic nature of the dienophile used, the reaction of **6** with other dienophiles was examined. Although longer reaction times than with DMAD were required, the Diels−Alder reaction of diene **6** with other differently functionalized acetylenic compounds (e.g. $Me_3SiC{\equiv}CCHO$, $PhSO_2C{\equiv}CH$) took place with similar *syn:anti* stereoselectivity. No appreciable reaction of **6** with sterically more demanding dienophiles such as methyl fumarate, methyl maleate, or maleic anhydride was observed under the same reaction conditions used with DMAD. Higher temperatures or the use of Lewis acid conditions promoted extensive isomerization of the diene double bonds.[15] As an exception, the Diels−Alder reaction of **6** with tetra-

CH at δ 5.82 ppm gave a NOE enhancement for the Me-8aβ at 0.95 ppm and the H-2β at 1.9 ppm. A similar stereochemical result has been recently observed in the addition of other Grignard reagents to the ketone **4**; see: Drew, M. G. B.; Harwood, L. M.; Jahans, A.; Robertson, J.; Swallow, S. *Synlett* **1999**, 185.

(9) By integration of the =CH signals for both adducts which are clearly resolved in the ^{1}H NMR spectrum of the mixture (δ 5.64 ppm for the major isomer and δ 5.50 ppm for the minor one).

(10) Arséniyadis, S.; Rodriguez, R.; Spanevello, R.; Camara, J.; Thompson, A.; Guittet, E.; Ourisson, G. *Tetrahedron* **1992**, *48*, 1255.

(11) Abad, A.; Agulló, C.; Arnó, M.; Marin, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2193.

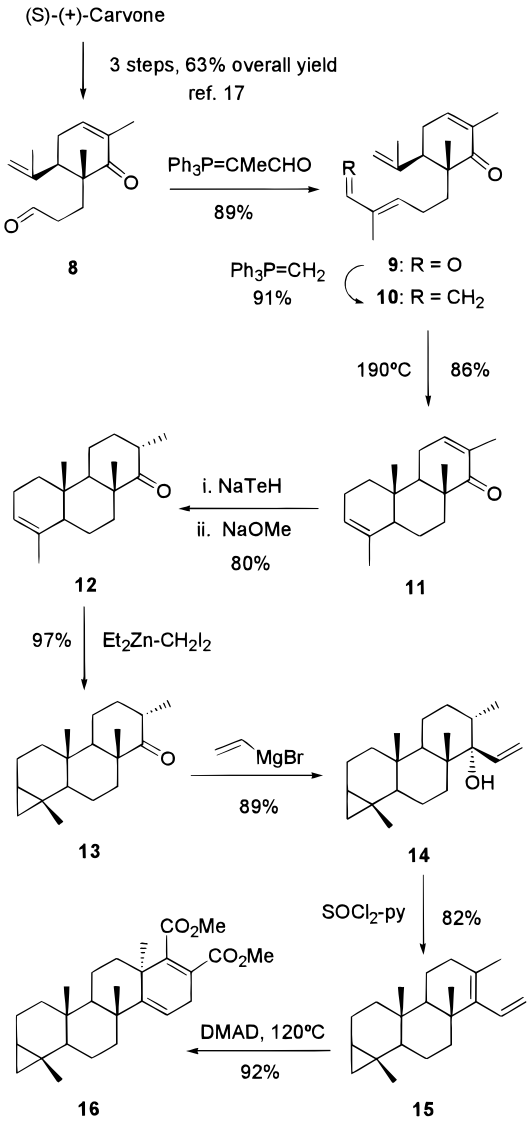
(12) Weibel, J. M.; Heissler, D. *Tetrahedron Lett.* **1994**, *35*, 473.

(13) Fallis, A. G.; Yee-Fung, L. π-Facial Diastereoselection in Diels−Alder Cycloadditions and Related Reactions: Understanding Planar Interactions and Establishing Synthetic Potential. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press Inc.: Greenwich, CT, 1993; Vol. 3, p 1.

(14) The geometry of the two [4 + 2]-cycloadducts was also optimized using molecular mechanics (MM2 force field) and semiempirical (AM1 and PM3 Hamiltonians) methods. The result of these calculations indicates that the *anti*-adduct is the most stable one (between 0.6 and 1.3 kcal/mol; see Figure 2 of the Supporting Information for the optimized structures of the adducts). On the basis of these data, a possible thermodynamic control of this Diels−Alder reaction seems unlikely.

(15) This circumstance has also been observed in the Diels−Alder reaction of related monocyclic dienes with ethylenic dienophiles; see: Jalali-Naini, M.; Guillerm, D.; Lallemand, J. Y. *Tetrahedron* **1983**, *39*, 749. For these conformationally more mobile monocyclic systems a combination of high-pressure and Lewis acid-catalyzed conditions has been used to promote the cycloaddition reaction; see: (a) Engler, T. A., Sampath, U.; Naganathan, S.; Vander Velde, D.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712. (b) Mayelvaganan, T.; Hadimani, S. B.; Shreeshailkumar, B.; Bhat, S. V. *Tetrahedron*, **1997**, *53*, 2185 and references therein.

Scheme 4



cyanoethylene as dienophile took place under very smooth conditions (e.g.: THF, room temperature, 48 h) to give a roughly 1:1 mixture of *anti*- and *syn*-adducts in nearly quantitative yield. However it has been shown that this highly reactive dienophile reacts by an aziridinium imide (1,4-zwitterion) mechanism, and thus, to draw conclusions from this reaction about the influence of the ethylenic nature of the dienophile in the stereochemical course of the Diels−Alder reaction of **6** does not seem reasonable.

Concurrently with the transformation described above we also studied the Diels−Alder reaction of the diene **15** with DMAD as a possible approach to the construction of the scalarane skeleton (Scheme 4).[16] The synthesis of the diene **15** commences with the preparation of the tricyclic ketone **12**, which is effected from (*S*)-(+)-carvone through the known keto aldehyde **8**,[17] following a similar route previously followed by us and others[18] for the preparation of related polycyclic systems.

Chemoselective Wittig reaction of the aldehyde group of **8** with (α-formylethylidene)triphenylphosphorane gave the chain-extended aldehyde **9**, which by Wittig methylenation under the usual conditions gave the triene **10** in 81% overall yield for the two steps. Heating a solution of **10** in toluene and a small amount of propylene oxide in a sealed tube at 185 °C for 6 days stereoselectively afforded the *trans-anti-trans* tricyclic ketone **11** in 86% yield. The reduction of the enone moiety of **11** with sodium tellurium hydride gave a mixture of epimeric ketones, which were equilibrated to the thermodynamically more stable equatorial methyl ketone **12** by sodium methoxide treatment. This ketone, obtained in 80% overall yield from the enone **11**, was then stereoselectively cyclopropanated under standard Simmons−Smith cyclopropanation conditions in very high yield. This was an indirect way of introducing the characteristic geminal dimethyl group that exists at the A ring of many natural scalaranes.

Completion of the synthesis of the diene **15** from **13** was finally effected by following the same protocol used for the previously described conversion of **4** into **6**. Thus, treatment of the ketone **13** with vinylmagnesium bromide and subsequent exposure to thionyl chloride−pyridine afforded the expected diene **15** in 73% overall yield.

With the diene **15** readily at hand, we tried its Diels−Alder reaction with DMAD. Heating a mixture of this diene and DMAD at 120 °C overnight cleanly afforded an approximately 95:5 mixture of Diels−Alder adducts in 92% yield after chromatographic purification of the crude product. Crystallization of this mixture from MeOH furnished the major adduct practically free of the minor one. Not unexpectedly, with knowledge of the previous result obtained in the Diels−Alder reaction of **6**, the structure **16** was assigned, on the basis of its spectroscopic data, to the major adduct obtained. Both Diels−Alder adducts **7** and **16** showed ^{1}H and ^{13}C NMR spectroscopic data that were superimposable on all the signals associated with their common structural features.[19]

In conclusion, the direction of the attack observed in the thermal Diels−Alder reaction of polycyclic 1,3-dienes **6** and **15** with DMAD is contrary to the expected α-approach of the dienophile, *anti* to the angular methyl groups. Consequently, the strategy outlined in Scheme 2, successfully used previously for the synthesis of bicyclic drimane sesquiterpenes, is not useful for the preparation of higher terpenes possessing spongiane (**2**) or scalarane (**3**) structures.[20]

Experimental Section[21]

(4a*S*,8a*S*,1*R*,2*R*)-2,5,5,8a-Tetramethyl-1-vinylperhydro-1-naphthtalenol (5). A solution of the ketone **4** (510 mg, 2.45 mmol) (prepared as described in ref 7; see also Supporting Information) in THF (13 mL) was treated at −78 °C with a 1 M solution of vinylmagnesium bromide in THF (4.9 mL, 4.9 mmol).

(16) The Diels−Alder reaction of a related diene with DMAD has been previously described; see: Nakano, T.; Hernández, M. I.; Martín, A.; Medina, J. D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1349. It follows from our work described here that the stereochemistry assigned by these authors to the Diels−Alder adduct prepared by them is incorrect and must be inverted at C-13 (terpene numbering; see ref 1b), thus making the work described in that paper the synthesis of a 13-episcalarane system.

(17) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Org. Chem.* **1998**, *63*, 5100.

(18) (a) Rawal, V. H.; Iwasa, S. *Abstracts of Papers*; 204th National Meeting of the American Chemistry Society, Washington, DC; American Chemical Society: Washington, DC, 1992; ORGN 35. (b) Shing, T. K. M.; Jiang, Q.; Mak, T. C. W. *J. Org. Chem.* **1998**, *63*, 2056 and literature cited therein.

The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 30 min. The mixture was diluted with saturated aqueous NH_4Cl solution and extracted with hexane. The combined organic phases were washed with brine, dried, and concentrated. The residue was purified by chromatography, using 95:5 hexanes−ether as eluent, to afford the alcohol **5** (463 mg, 80%): mp 35−36 °C (from cold pentane); $[\alpha]^{22}_D$ −14.3 (c 10.2, $CHCl_3$); IR (KBr) 3600 cm^{-1}; ^1H NMR (199.95 MHz, $CDCl_3$) δ 5.82 (1H, dd, *J* 17.2, 10.8), 5.13 (1H, dd, *J* 10.8, 1.6), 5.04 (1H, dd, *J* 17.2, 1.6), 0.95 (3H, s), 0.86 (3H, s), 0.81 (3H, s), 0.70 (3H, d, J 6.7); HRMS calcd for $C_{16}H_{28}O$ 236.2140, found 236.2147. This was followed by the (1*S*)-epimer of **5** (28 mg, 5%): $[\alpha]^{22}_D$ −10.7 (*c* 9.9, $CHCl_3$); IR (film) 3511 cm^{-1}; ^1H NMR (299.95 MHz, $CDCl_3$) δ 6.20 (1H, dd, *J* 16.8, 11.5), 5.24 (1H, dd, *J* 11.5, 1.9), 5.23 (1H, dd, *J* 16.8, 1.9), 1.05 (3H, s), 0.84 (3H, s), 0.83 (3H, s), 0.70 (3H, d, J 6.6); HRMS calcd for $C_{16}H_{28}O$ 236.2140, found 236.2135.

(4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-vinylnaphthalene (6). To a solution of the alcohol **5** (450 mg, 1.9 mmol) in anhydrous pyridine (4 mL) was added dropwise thionyl chloride (0.18 mL, 2.09 mmol) at −30 °C. The reaction mixture was allowed to warm to −10 °C during 1 h and then diluted with hexane. The organic layer was washed with diluted hydrochloric acid, aqueous $NaHCO_3$, and brine. Drying and evaporation of the solvent gave an oily residue. This was purified by chromatography, using 95:5 hexanes−ether as eluent, to give the diene **6** (374 mg, 90%) as a relatively volatile colorless oil: $[\alpha]^{22}_D$ +85 (*c* 6, $CHCl_3$); IR (film) 3091, 1621, 915 cm^{-1}; ^1H NMR (200.13 MHz, $CDCl_3$) δ 6.10 (1H, dd, *J* 17.5, 11.1), 5.21 (1H, dd, *J* 11.1, 2.9), 4.87 (1H, dd, *J* 17.5, 2.9), 1.62 (3H, s), 0.97 (3H, s), 0.87 (3H, s), 0.82 (3H, s); HRMS calcd for $C_{16}H_{26}$ 218.2034, found 218.2033.

Dimethyl (1*S*,7*S*,10*S*)-1,7,11,11-Tetramethyltricyclo-[8.4.0.0^{2,7}]tetradeca-2,5-diene-5,6-dicarboxylate (7). A mixture of diene **6** (68.4 mg, 0.316 mmol) and recently distilled DMAD (100 μL, 0.632 mmol) was sealed in a tube under argon and heated at 110 °C for 24 h. After cooling, the tube was opened and the excess of DMAD was eliminated at reduced pressure. The residue obtained was purified by chromatography eluting with 95:5 hexanes−ether to give an approximately 95:5 mixture of the Diels−Alder adducts (105 mg, 95%), as determined by integration of the =CH signals for both adducts in the ^1H NMR spectrum of the mixture. Recrystallization from hexane−dichloromethane gave pure **7**: mp 154−156 °C; $[\alpha]^{22}_D$ +16 (*c* 2.4, $CHCl_3$); IR (KBr) 1720, 1660, 1630 cm^{-1}; ^1H NMR (299.95 MHz, $CDCl_3$) δ 5.64 (1H, dd, *J* 6.5, 1.9), 3.81 (3H, s), 3.73 (3H, s), 3.14 (1H, dd, *J* 21.8, 6.5), 2.77 (1H, dd, *J* 21.8, 1.9), 1.31 (3H, s), 1.05 (3H, s), 0.91 (3H, s), 0.85 (3H, s); HRMS calcd for $C_{22}H_{32}O_4$ 360.2301, found 360.2311.

(1b*S*,4*S*,5*S*,7b*S*,9a*S*,1a*R*,3a*R*,7a*R*)-1a,3a,5,7b-Tetramethyl-4-vinylperhydrocyclopropa[a]phenanthren-4-ol (14). Ethenylation of ketone **13** (136 mg, 0.50 mmol) (prepared as described in the Supporting Information) by treatment with vinylmagnesium bromide (1 mL of a 1 M solution in THF, 1 mmol) in THF (4 mL) in the same way described for **4** afforded, after chromatographic purification using 9:1 hexanes−ether as eluent, the alcohol **14** (124 mg, 89%) as a white solid: mp 106.5−107 °C (from MeOH); $[\alpha]^{25}_D$ +38.4 (c 1.3, $CHCl_3$); IR (KBr) 3635, 1454, 1363, 996, 936 cm^{-1}; ^1H NMR (299.95 MHz, $CDCl_3$) δ 5.83 (1H, dd, *J* 16.7, 11.5), 5.16 (1H, dd, *J* 16.7, 1.7), 5.15 (1H, dd, *J* 11.5, 1.7), 1.9 (2H, m), 1.01 (3H, s), 0.94 (3 H, s), 0.79 (3H, s), 0.70 (3H, d *J* 6.6), 0.5 (1H, m), 0.4 (1H, dd, *J* 9.0, 3.6), −0.09 (1H, dd, *J* 6.0, 3.6); HRMS calcd for $C_{21}H_{34}O$ 302.2609, found 302.2604.

(1*S*,10*S*,13*S*,2*R*,7*R*,11*R*)-1,5,7,11-Tetramethyl-6-vinyltetracyclo[8.5.0.0^{2,7}.0^{11,13}]pentadec-5-ene (15). This compound was prepared by treatment of **14** (124 mg, 0.42 mmol) with pyridine (1.6 mL) and thionyl chloride (40 μL, 0.42 mmol), as described above for the synthesis of **6**. Extraction with hexane and workup of the extract afforded a residue, which was purified by chromatography, using 9:1 hexanes−ether as eluent, to give diene **15** (96 mg, 82%) as a colorless oil: $[\alpha]^{25}_D$ −10.6 (*c* 1.7, $CHCl_3$); IR (KBr) 3073, 3047, 1619, 915, 846 cm^{-1}; ^1H NMR (299.95 MHz, $CDCl_3$) δ 6.10 (1H, ddd, *J* 17.6, 11.2, 1), 5.22 (1 H, ddd, *J* 11.2, 2.9, 1), 4.90 (1H, dd, *J* 17.6, 11.2), 1.61 (3H, s), 1.02 (3H, s), 0.94 (3H, s), 0.81 (3H, s), 0.5 (1H, m), 0.42 (1H, dd, *J* 9.3, 3.6), −0.05 (1H, dd, *J* 6.0, 3.6); HRMS calcd for $C_{21}H_{32}$ 284.2504, found 284.2501.

Dimethyl (2*S*,5*S*,8*S*,1*R*,7*R*,11*R*,17*R*)-2,7,11,17-tetramethylpentacyclo[9.8.0.0^{2,8}.0^{5,7}.0^{12,17}]nonadeca-12,15-diene-15,16-dicarboxylate (16). In the same manner as described above for the conversion of **6** into **7**, a mixture of **15** (36.8 mg, 0.13 mmol) and DMAD (32 μL, 0.26 mmol) was heated at 120 °C for 15 h. Chromatography of the crude product, using 8:2 hexanes−ether as eluent, yielded the adduct **16** (50.7 mg, 92%) as a solid, which was contaminated, as shown by its ^1H NMR spectrum, by approximately 5% of the epimeric adduct at C-13. Pure **16** was obtained by crystallization from MeOH: mp 117.5−118 °C; $[\alpha]^{25}_D$ +30 (*c* 9.4, $CHCl_3$); IR (KBr) 1723 cm^{-1}; ^1H NMR (299.95 MHz, $CDCl_3$) δ 5.62 (1H, dd, *J* 6.3, 1.7), 3.79 (3H, s), 3.71 (3 H, s), 3.14 (1H, dd, *J* 21.7, 1.7), 2.76 (1H, dd, *J* 21.7, 6.6), 2.09 (1H, ddd, *J* 12.8, 3.8, 3.8),1.9 (1H, m),1.57 (1H, m), 1.25 (3H, s), 0.97 (3H, s), 0.89 (3 H, s), 1.10 (3 H, s), 0.54 (1H, m), 0.5 (1H, m), 0.41 (1H, dd; *J* 10.0, 3.6), −0.04 (1H, dd, J 6.4, 3.6); HRMS calcd for $C_{27}H_{38}O_4$ 426.2770, found 426.2774.

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Supporting Information Available: ^1H NMR spectra of compounds **4**−**16**, tables of ^{13}C NMR data of compounds **4**−**7** (Table I), **8**−**10** (Table II), and **11**−**16** (Table III), X-ray structural analysis of compound **7** containing crystal data, tables of atomic coordinates, thermal parameters, and bond lengths and angles, and the labeled structure (Figure 1 and Tables IV−IX), optimized geometries and HF/STO-3G transition structures for *syn*- and *anti*-adducts of the reaction of **6** with DMAD (Figures 2 and 3), and spectroscopic data and detailed experimental procedures for the preparation of compounds **4** and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) It is noteworthy that the Diels−Alder reaction of the 1,3-diene containing the double bond in the A ring (prepared from **12** following the same procedure previously described for the conversion of **4** into **6**) took place with identical efficacy and stereoselectivity, but in this case and previously to the Diels−Alder reactions as showed control experiments, the ene reaction of the A ring olefin moiety with DMAD as enophile also occurred. Interesting, initial biological evaluation revealed that this compound possesses promising antifungal and β-glucuronidase inhibition activities. These results should be published elsewhere.

(20) However, the results obtained in this work are of interest since they could allow the preparation of tricyclic terpenoid systems with the uncommon *trans-anti-cis* arrangement. For a relevant compound of this type, see: Manes, L. V.; Crews, P.; Kernan, M. R.; Faulkner, D. J.; Fronczek, F. R.; Gandour, R. D. *J. Org. Chem*. **1988**, *53*, 570. This possibility is being studied in our laboratory.

(21) For general experimental information, please see ref 17.