Efficient Stereocontrolled Total Syntheses of Racemic and Natural Brefeldin-A

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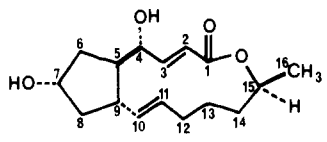
Abstract: Brefeldin-A, an antibiotic fungal metabolite, has been obtained in both racemic and natural forms through a direct approach that employs norbornenone and 6-heptyn-2-ol as the basic starting materials.

Brefeldin-A (as decumbin) was first isolated in 1958 from *Penicillium decumbens* by Singleton, Bohonos, and Ullstrup.[1a] The metabolite has subsequently been found in cultures of *Penicillium cyaneum*,[1b] *Penicillium brefeldianum*,[1c] and *Ascochyta imperfecta*,[1d] as well as in those of a wide variety of other organisms.[1e-i] The identity[1d,2] of the metabolites, however, has not in all cases been immediately apparent, thus producing for this compound the names cyanein[1b] and ascotoxin,[1d] in addition to decumbin[1a] and brefeldin-A.[1c] Work[1,2] on the elucidation of the structure and stereochemistry, carried out over 14 years, was finally concluded through a definitive X-ray crystallographic study by Weber, Hauser, and Sigg[3] in 1971, indicating formula **1*** [4] for (+)-brefeldin-A.



(+)-Brefeldin-A **1***

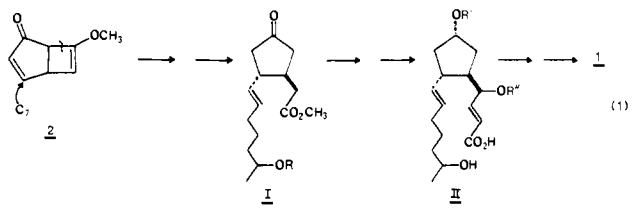
Extensive biological testing, largely effected by Betina and collaborators, has established a wide range of biological activity for this compound, including antiviral,[5] antifungal,[6] antimitotic,[7a] and antitumor[1c,7b] effects. Although it has been found that brefeldin-A is derived completely from acetate, several aspects of its biosynthesis remain obscure in spite of considerable investigation.[8]

Synthetic studies on natural brefeldin-A by Corey and coworkers[9] led to the discovery of certain selective reactions, which subsequently not only facilitated this group's first total synthesis of racemic brefeldin-A[10a] but also aided much of the synthetic effort that has followed in this area.[10b-k] This rather considerable effort in a number of laboratories has to date produced several additional syntheses of racemic brefeldin-A[10c-g,i] as well as a lengthy one[10f] of (+)-brefeldin-A, the naturally occurring form of this substance.

In this paper we detail our successful synthesis[10d] of racemic brefeldin-A and, in addition, disclose an efficient and highly stereoselective synthesis of (+)-brefeldin-A.

Discussion

Synthesis of Racemic Brefeldin-A. Our own interest in this natural product stemmed from a prostaglandin synthesis program.[11] Enone **2**, a photoproduct from α-tropolone methyl ether, had served in this program as a versatile intermediate, and it appeared that it might be suitable as well for use in the synthesis of brefeldin-A (eq 1). The folded bicyclic enone had been shown



(1)

to suffer several highly stereoselective conjugate additions, and consequently, it was envisioned that an appropriately functionalized 7-carbon unit could also be joined in this manner; a retro-Claisen

(1) (a) Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature (London)* **1958**, *181*, 1072. (b) Betina, V.; Nemec, P.; Dobias, J.; Barâth, A. *Folia Microbiol. (Prague)* **1962**, *7*, 353. (c) Härri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Tamm, Ch. *Helv. Chim. Acta* **1963**, *46*, 1235. See also: Nishimura, S. *Jpn. Kokai Tokkyo Koho 72*, 25,385 (*Chem. Abstr.* **1973**, *78*, 41571r); Nishimura, S. *Jpn. Kokai Tokkyo Koho 78*, 01,357 (*Chem. Abstr.* **1978**, *88*, 150595d). (d) Suzuki, Y.; Tanaka, H.; Aoki, H.; Tamura, T. *Agric. Biol. Chem.* **1970**, *34*, 395. (e) Betina, V.; Fuska, J.; Kjaer, A.; Kutkova, M.; Nemec, P.; Shapiro, R. H. *J. Antibiot., Ser. A* **1966**, *19*, 115 (*Penicillium simplicissimum*). (f) Mirrington, R. N.; Ritchie, E.; Shoppee, C. W.; Sternhell, S.; Taylor, W. C. *Aust. J. Chem.* **1966**, *19*, 1265 (*Nectria radicicola*). (g) Coombe, R. G.; Jacobs, J. J.; Watson, T. R. *Ibid.* **1968**, *21*, 783 (*Curvularia lunata, C. subulata*). (h) Mortimer, P. H.; Di Menaa, M. E.; White, E. P. *Mycotoxic Fungi, Mycotoxins, Mycotoxicoses* **1978**, *2*, 219. (*Chem. Abstr.* **1978**, *89*, 1453z) (*Phoma herbarum*). (i) Entwistle, I. D.; Howard, C. C.; Johnstone, R. A. W. *Phytochemistry* **1974**, *13*, 173. Howard, C. C.; Johnstone, R. A.; Entwistle, I. D. *Ger. Offen.* 2 325 330 (*Chem. Abstr.* **1974**, *80*, 69140q) (*Phyllosticta medicaginis*).

(2) Singleton, V. L.; Bohonos, N. *Agric. Biol. Chem.* **1964**, *28*, 77. Sigg, H. P. *Helv. Chim. Acta* **1964**, *47*, 1401. Betina, V.; Nemec, P.; Kovač, S.; Kjaer, A.; Shapiro, R. H. *Acta Chem. Scand.* **1965**, *19*, 519.

(3) Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763.

(4) An asterisk with a compound number signifies that a single enantiomer is being depicted with absolute stereochemistry as indicated. Compounds **20***–**23*** have the 15*S* configuration.

(5) Tamura, G.; Ando, K.; Suzuki, S.; Takatsuki, A.; Arina, K. *J. Antibiot.* **1968**, *21*, 160. Takatsuki, A.; Yamaguchi, I.; Tamura, G.; Misato, T.; Arima, K. *Ibid.* **1969**, *22*, 442.

(6) Betina, V.; Drobnica, Ľ.; Nemec, P.; Zemanova, M. *J. Antibiot., Ser. A* **1964**, *17*, 93. Betina, V.; Betinova, M.; Kutkova, M. *Arch. Mikrobiol.* **1966**, *55*, 1. Hayashi, T.; Takatsuki, A.; Tamura, G. *J. Antibiot.* **1974**, *27*, 65.

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(9) (a) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S. *J. Am. Chem. Soc.* **1975**, *97*, 654. (b) Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4701.

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(11) Greene, A. E.; Teixeira, M. A.; Barreiro, E.; Cruz, A.; Crabbé, P. *J. Org. Chem.* **1982**, *47*, 2553.

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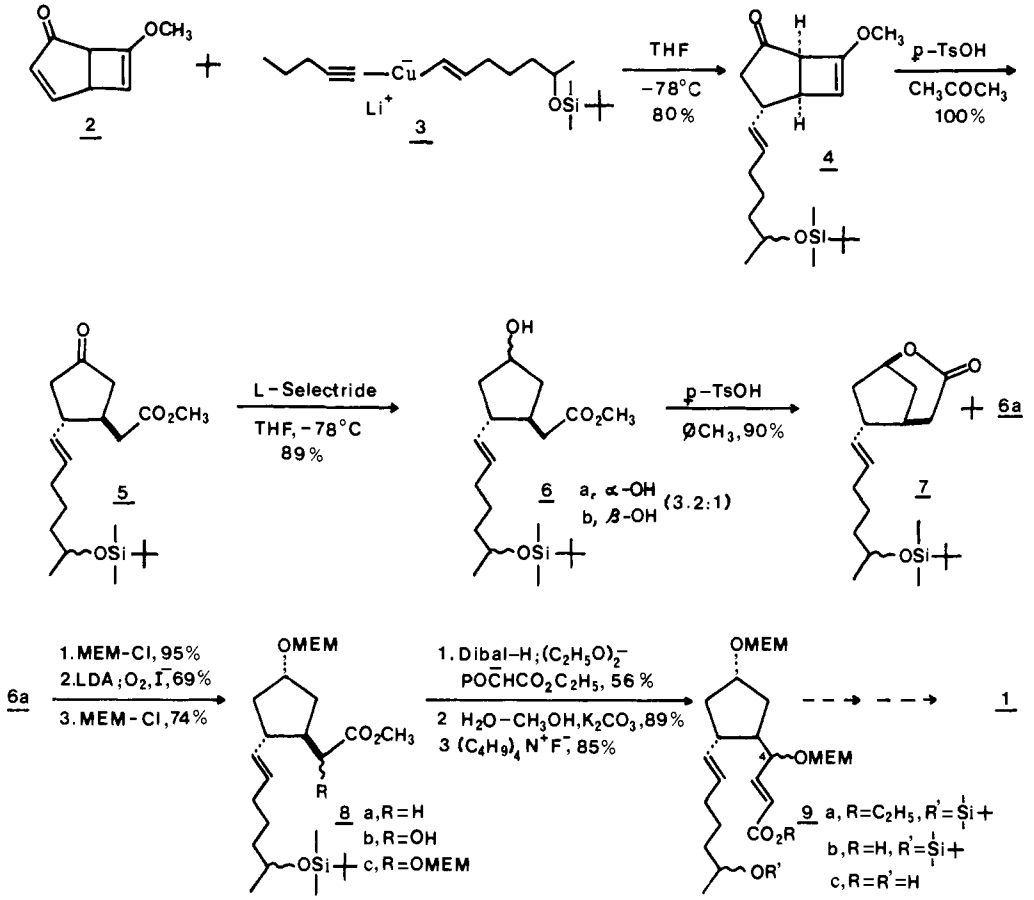
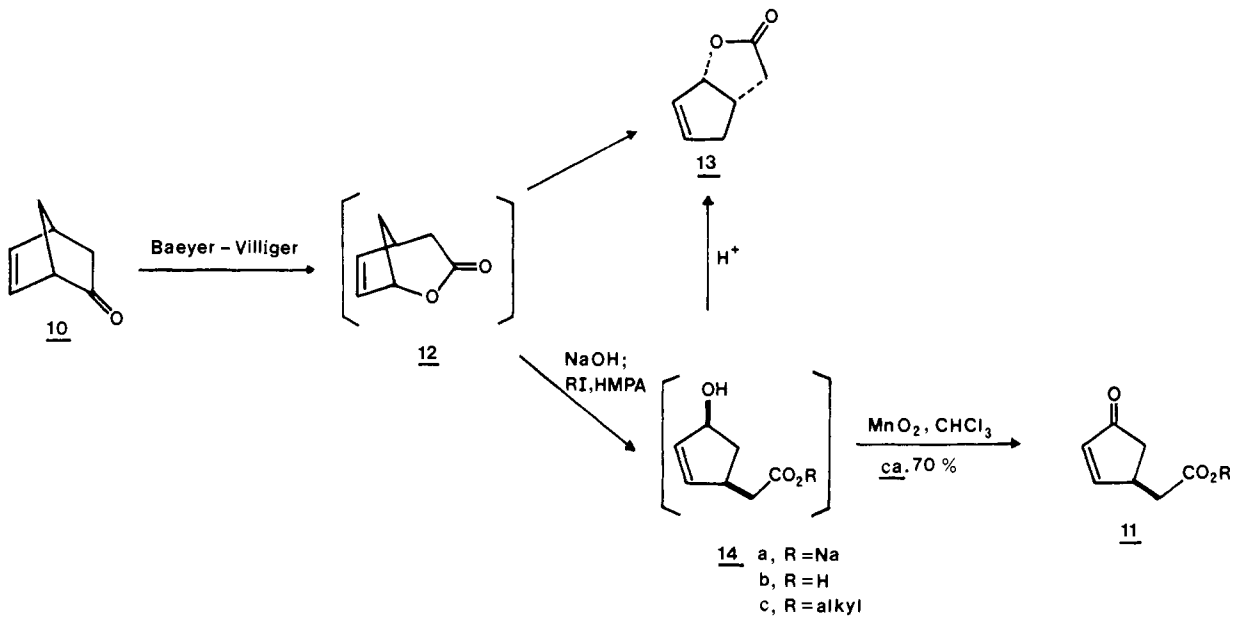
Scheme I



Scheme II

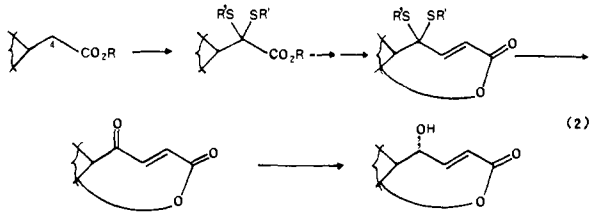


ring cleavage would then furnish a carbomethoxymethyl side chain (I) from which the γ-hydroxycrotonic acid portion of brefeldin-A could be built after suitable modification of the ring functionality. Lactonization of the seco derivative II and removal of any remaining protecting groups would then yield brefeldin-A (**1**).

Reduced to practice, this overall plan proved to be viable. The total synthesis[10c] using this strategy is outlined in Scheme I. However, the synthesis was completed only in a formal sense, being made to intersect with Corey and Wollenberg's synthesis,[10a] which was published during our work.

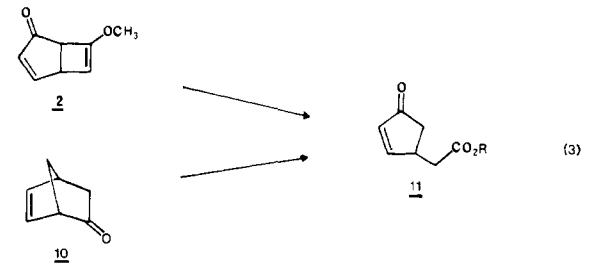
A number of shortcomings were clearly revealed over the course of this work. Foremost was that of having an epimeric mixture of protected alcohols at C-4 (brefeldin-A numbering), which not only necessitated a somewhat cumbersome procedure for establishing the correct C-4 stereochemistry but also complicated considerably chromatographic purifications and spectral analyses. It seemed that a suitably protected carbonyl at C-4 in lieu of a protected hydroxyl group might alleviate these problems in that no new asymmetric center(s) would have to be created, and after lactonization, the C-4 α-OH could be stereoselectively generated

from the corresponding ketone by reduction, as demonstrated by Corey and Wollenberg.[9b,12] A thioketal-protected ketone offered, in this particular context, the important additional advantages over most other forms of ketone protection (as well as the free carbonyl) of great ease of introduction and stability under a variety of reaction conditions and yet facile, selective hydrolytic cleavage. Thus, the sequence of transformations shown in eq 2 was envisaged.



(2)

Additionally, in that the ultimate objective of our work was a synthesis of chiral brefeldin-A, an alternative enone (replacing **2**) that could be fairly readily obtained in optically active form was desirable. While this problem could have been, in principle, solved by merely reversing the retro-Claisen and conjugate addition steps of the previous synthesis (Scheme I), thereby producing a resolvable intermediate (eq 3, **11**, R = H),[13] it seemed preferable



(3)

from a practical standpoint to generate this same chiral intermediate, if possible, from norbornenone.

The total syntheses of racemic brefeldin-A and (+)-brefeldin-A incorporating these synthetic strategies are described below.

Norbornenone (**10**) represented an ideal starting material, readily prepared on a multimole scale in 80–85% yield from cyclopentadiene and α-chloroacrylonitrile[14] and obtainable in optically active form.[15] Meinwald and co-workers[16] had shown a number of years ago that norbornenone in acetic acid containing peracetic acid engenders the expected lactone **12**, but only as the minor product, the major product being the allylically rearranged lactone **13** (Scheme II). The desired lactone **12** can be intercepted, however, as its hydroxy acid salt **14a** by effecting the Baeyer–Villiger reaction under basic conditions ($NaOH-H_2O_2$ in Et_2O-H_2O).[17] In contrast to recent literature reports,[18] we experienced considerable difficulty in the isolation of the relatively unstable[19] corresponding free hydroxy acid **14b** uncontaminated by less than substantial amounts of lactone **13**; therefore, the sodium salt **14a** was directly esterified in HMPA with any one of a number of different alkyl iodides (CH_3I, C_2H_5I, i-C_3H_7I, n-C_4H_9I).[20] Oxidation of the resultant crude hydroxy esters **14c** with activated manganese dioxide in chloroform then produced the corresponding enone esters **11**. Although the isopropyl and n-butyl esters were both easier to purify than the methyl and ethyl esters (invariably, ca. 10% of lactone **13** was present), the n-butyl ester proved to be distinctly superior to the isopropyl ester in terms of the yield and selectivity in the subsequent conjugate addition reaction and was therefore used in the synthesis. The overall yield from norbornenone of the enone ester **11** (R = C_4H_9) on large scale runs was 70%.

The conjugate addition to enone **11** (R = C_4H_9) of the C-10 to C-16 carbon unit of brefeldin-A was carried out in the presence of tris(dimethylamino)phosphine (HMP) employing the earlier used[10ac,d] mixed cuprate reagent **3** (Scheme III), the preparation of which is outlined in Scheme IV. The stannane **19** was shown by ^{13}C NMR to consist of ca. 85% of the desired E isomer and ca. 15% of the unwanted Z isomer. However, the Z isomer in similar mixtures had been shown to undergo transmetalation with n-butyllithium significantly more slowly than the E isomer,[25] and consequently, by adding only 0.85 equiv of n-butyllithium to the mixture, the (E)-vinylstannane could be selectively transmetalated. Addition of this vinyllithium reagent to pentynylcopper in THF containing tris(dimethylamino)phosphine (HMP)[26] then generated the mixed cuprate reagent **3**, which was treated with enone **11** to give in up to 72% yield the desired conjugate addition product **20** as a ca. 1:1 mixture of diastereomers (vide infra). Approximately 3% of the corresponding 5,9-cis product was also isolated from this reaction.[27]

Reduction of keto ester **20** with L-Selectride[30] in THF at −78 °C engendered a mixture of C-7 α and β alcohols, which could not be resolved into more than one spot by thin-layer chromatography; however, the pure α-alcohol **21a** could be effectively

(12) Although a seco acid bearing an unprotected C-4 carbonyl was later lactonized (37% yield),[10e] we felt that a protected carbonyl would prove generally advantageous. It should be pointed out that in the C-4 reduction of nonlactonized monocyclic γ-oxocrotonates the *unnatural* C-4 epimer is favored over the natural by 4–5:1,[10e,i] thus ruling out reduction (and protection) prior to lactonization.

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(15) Asymmetric induction in hydroboration: (a) Mislow, K.; Berger, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 1956. (b) Sandman, D. J.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 2924. (c) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1976**, *15*, 12. Asymmetric induction in the Diels–Alder reaction: (d) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333. (e) Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 2418. (f) Sauer, J.; Kredel, J. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 989. (g) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 6359. (h) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (i) Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffat, F. *Tetrahedron Lett.* **1981**, 2545. Resolution: (j) Nakazaki, M.; Naemura, K.; Kondo, Y. *J. Org. Chem.* **1976**, *41*, 1229. (k) Lightner, D. A.; Beavers, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 2677. See also: (l) Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *Ibid.* **1961**, *83*, 3986. Microbial reduction: (m) Nakazaki, M.; Chikimatsu, H.; Naemura, K.; Asao, M. *J. Org. Chem.* **1980**, *45*, 4432. Recently, optically pure methyl (1*S*)-*exo*-norbornenecarboxylate has been obtained through a Diels–Alder reaction between cyclopentadiene and a derivative of arabinose. However, large amounts of (−)-norbornenone cannot be readily secured by using this procedure. See: Horton, D.; Machinami, T. *J. Chem. Soc., Chem. Commun.* **1981**, 88.

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(19) See, for example: Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C-L. J. *J. Org. Chem.* **1978**, *43*, 4178. Grieco, P. A.; Ohfune, Y. *Ibid.* **1980**, *45*, 2251. Grieco, P. A.; Williams, E.; Sugahara, T. *Ibid.* **1979**, *44*, 2194.

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(23) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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(25) (a) Chen, S. M.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450. (b) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.

(26) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

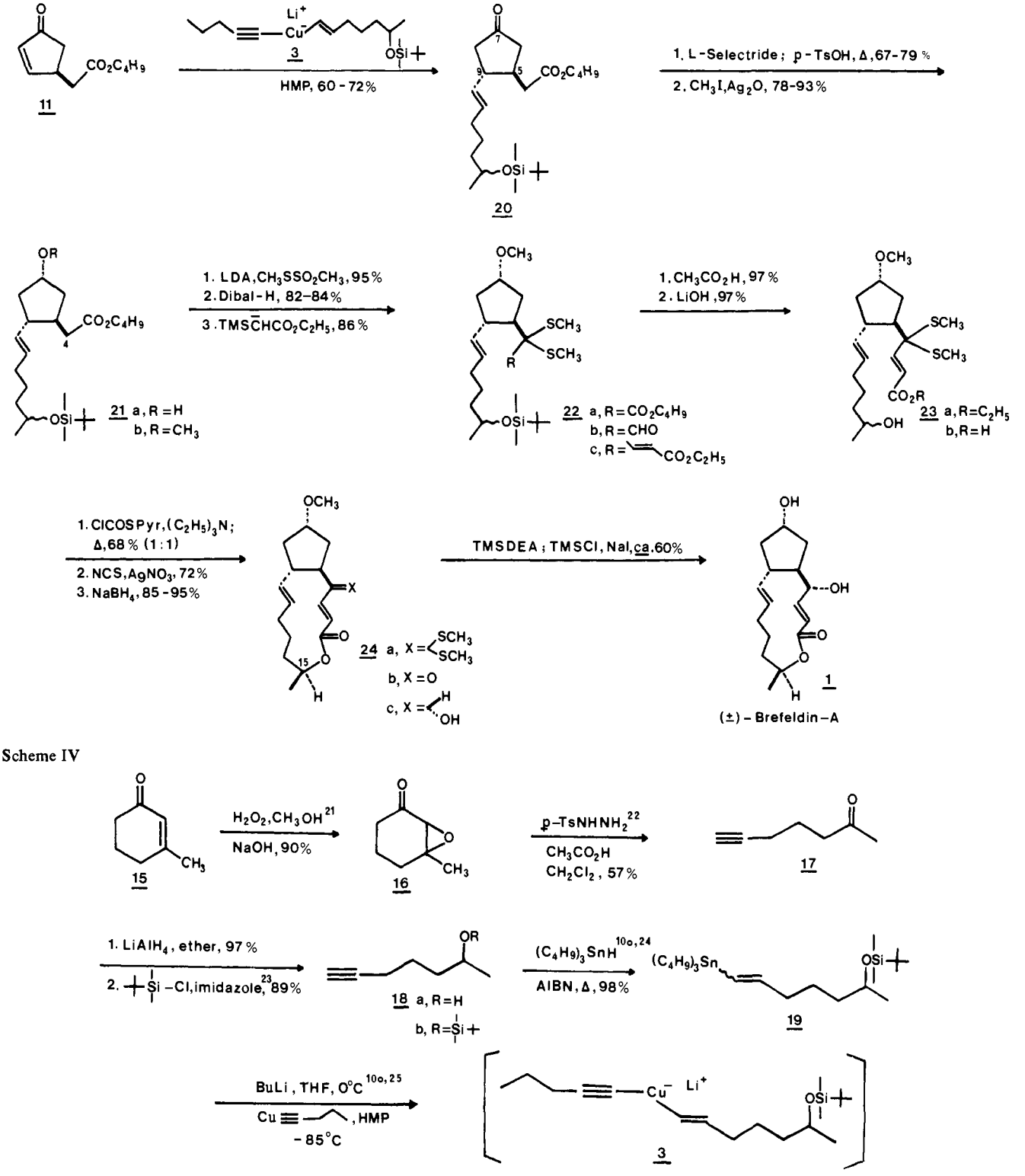
(27) The isopropyl ester underwent a similar transformation to give a 61% yield of the trans adduct and an 11% yield of the cis adduct. In the absence of HMP, however, the cuprates formed with pentynylcopper,[26] (3-methoxy-3-methylbutynyl)copper,[28] and (3,3-dimethylbutynyl)copper[29] produced the trans adduct in only 30–45% yield. As might be expected on the basis of the relative inertness of the (Z)-vinylstannane,[25] the use of 1.0 equiv of n-butyllithium in the cuprate preparation resulted in the formation of significant amounts of the corresponding n-butyl addition product.

(28) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(29) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

(30) L-Selectride is a registered trademark of Aldrich Inc., Milwaukee, WI.

Scheme III



Scheme IV

obtained in 67% yield from the mixture by heating with *p*-toluenesulfonic acid in toluene followed by simple silica gel chromatographic separation from the resultant lactonized β-alcohol **7** (25% yield). The latter could be transformed in a straightforward manner[31] to α-alcohol **21a** in 47% yield, thus raising the overall yield of this alcohol from ketone **20** to 79%.

Next, the α alcohol was converted in high yield to the methyl ether **21b** with silver oxide and methyl iodide in refluxing acetonitrile.[33] Although the stereoselectivity in the forthcoming C-4 reduction could have been adversely affected by the use of this protecting group in lieu of the larger and better coordinating (methoxyethoxy)methyl[9b] or methoxymethyl[10e] groups, we were attracted by the greater stability of this group over the range of

(31) The lactonized β-alcohol could be converted to the α-alcohol **21a** in 47% overall yield by successive treatment as follows: NaOH; CH_2N_2; DEAD, Ph_3P, AcOH;[32] NaOH, *n*-BuI, HMPA.[20]

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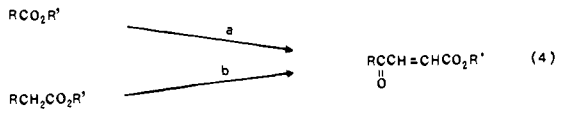
conditions required for the subsequent steps in the synthesis. An additional incentive for this selection over the previously employed[10c] (methoxyethoxy)methyl group stemmed from the observation that this latter protecting group appeared to interact detrimentally, undoubtedly owing to its excellent coordinating ability,[34] in a number of oxidations and reductions performed on compounds similar to the intermediates we hoped to synthesize.

In that the best procedure for stereoselectively securing the C-4 α-hydroxyl appeared at the time to be (and still is) through reduction of 4-dehydrobrefeldin-A as the protected C-7 alcohol,[9b,10e] the construction of a ketone-protected γ-oxocrotonate unit that, after lactonization, could be selectively deprotected under mild conditions was next studied.[12,35] Although several methods,[10a,e,j,36] existed in the literature for transforming a carbalkoxyl group to a γ-oxocrotonate (eq 4, path a), there was a surprising



(4)

paucity of available procedures[10b,c,37] for effecting the required overall conversion of a carbalkoxymethyl to this unit (path b). In that it seemed a nonasymmetric, thioketal-protected C-4 carbonyl would be most effective (vide supra), ester **21b** was treated alternately[38] with lithium diisopropylamide (LDA) and methyl methanethiosulfonate[40] to effect a "one-pot" bis(methylsulfenylation),[41] yielding the desired thioketal **22a** in excellent yield. Very carefully controlled reduction of **22a** in toluene at ca. −110 °C produced directly the desired aldehyde **22b** in 82% yield.[42] The extreme sluggishness of the reaction between triethyl sodiophosphonoacetate and aldehyde **22b** prompted the examination of an alternative reagent, ethyl lithio(trimethylsilyl)acetate.[43] In THF at −35 °C, this reagent furnished the conjugated ester **22c**, exclusively *E*, in 86% yield. This very pleasing apparent total absence of the corresponding *Z* isomer (which would have two bulky groups in juxtaposition) is also found with analogues of **22b**[41] and with pinacolone;[43b] it is seemingly best explained through a mechanism in competition with (or excluding) the syn elimination pathway that involves an initial 1,3-carbon to oxygen migration of the silyl group followed by a stereoselective β elimination.[44]

Selective hydrolysis of the C-15 protecting group with aqueous acetic acid generated in 97% yield the hydroxy ester **23a**, which was saponified by using lithium hydroxide in aqueous methanol to give **23b** (97% yield) and set the stage for the key lactonization step. Of the various methods[45] examined employing several different model systems, the most effective procedure was clearly the experimentally simple "double-activation" method described by Corey and Nicolaou,[45g] as later modified by Corey and Clark.[45h] Application of this procedure to the hydroxy acid mixture **23b** provided in 68% yield a 1:1 mixture of diastereomeric lactones,[46] which could be quite easily separated by silica gel chromatography (R_f 0.38 and 0.48).

The appropriateness of the particular combination of protecting groups used in this approach is evidenced by the directness of the conclusion of the synthesis. The more polar of the above isomers **24a** was treated with *N*-chlorosuccinimide in aqueous acetonitrile in the presence of silver nitrate[47] to afford in 72% yield the sensitive γ-oxocrotonate **24b** [R_f 0.30, δ 4.45 (C-15H)]. Similarly, the less polar isomer was converted to the corresponding γ-oxocrotonate (R_f 0.37, δ 5.00). Comparison of the relative polarities and C-15 proton chemical shifts of these products with those reported[10e] for 4-dehydrobrefeldin-A 7-methoxymethyl ether (R_f 0.40, δ 4.68) and its C-15 epimer (R_f 0.45, δ 5.23) allowed a tentative (correct) C-15 stereochemical assignment to be made. Thus, the more polar γ-oxocrotonate **24b** was treated with sodium borohydride in methanol at −78 °C to give alcohol **24c** as a unique, highly crystalline product in 85–95% yield.[48] Following silylation of the C-4 hydroxyl, conveniently effected with (trimethylsilyl)diethylamine,[49] the C-7 methyl ether was cleaved by using chlorotrimethylsilane and anhydrous sodium iodide in dry acetonitrile[50] under very precisely controlled conditions to afford crystalline racemic brefeldin-A (**1**) in approximately 60% yield. This material was indistinguishable spectroscopically (IR, NMR, MS) and chromatographically (TLC, HPLC) from the natural product.

Synthesis of Natural Brefeldin-A. The same convergent approach, employing the appropriate chiral components, was envisaged for the synthesis of natural brefeldin-A.

(34) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(35) An alternative strategy of introducing a C-4 hydroxyl (or carbonyl) through γ-oxidation *after* lactonization (which also would have eliminated several steps of the previous synthesis) failed to produce any useful results in spite of the diverse methods examined.

(36) Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. *Tetrahedron Lett.* **1978**, 2371 and references cited therein.

(37) Ortiz de Montellano, P. R.; Hsu, C. K. *Tetrahedron Lett.* **1976**, 4215.

(38) It was found that 2 equiv of both LDA and methyl methanethiosulfonate could not be present at the outset in that destruction of the reagent(s) apparently occurs faster than the introduction of the second methylthio group, in contrast with reported results obtained with LDA and either diphenyl disulfide[39a,b] or phenyl benezenethiosulfonate.[39c] Although in a model system bis(phenylsulfenylation) with LDA and phenyl benzenethiosulfonate could also be achieved in nearly quantitative yield, conditions for a direct, one-step hydrolysis of the thioketal group in the homologated ester (to give the ultimately required γ-oxocrotonate) could only be found for the dimethyl thioketal.

(39) (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (b) Trost, B. M.; Massiot, G. S. *Ibid.* **1977**, *99*, 4405. (c) Trost, B. M.; Mao, M. K. T. *Tetrahedron Lett.* **1980**, 3523. See, however: Gassman, P. G.; Balchunis, R. J. *J. Org. Chem.* **1977**, *42*, 3236. Yee, Y. K.; Schultz, A. G. *Ibid.* **1979**, *44*, 719.

(40) Backer, H. J. *Bull. Soc. Chim. Belg.* **1953**, *62*, 3 (*Chem. Abstr.* **1954**, *48*, 5075c). This is also available from Aldrich.

(41) Greene, A. E.; Le Drian, C.; Crabbé, P. *J. Org. Chem.* **1980**, *45*, 2713.

(42) Collins oxidation of the more polar material, separated on silica gel chromatographic purification of the aldehyde, yielded an additional 2% of **22b**.

(43) (a) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620. (b) Taguchi, H.; Shimoji, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2529. (c) Hartzell, S.; Sullivan, D. F.; Rathke, M. W. *Tetrahedron Lett.* **1974**, 1403. (d) Grieco, P. A.; Weng, C-L. J.; Burke, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 537.

(44) Larchevêque, M.; Debal, A. *J. Chem. Soc., Chem. Commun.* **1981**, 877. See also: Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* **1980**, 2861.

(45) See: (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. (b) Mukaiyama, T.; Narasaka, K.; Kikuchi, K. *Ibid.* **1977**, 441. Narasaka, K.; Yamaguchi, M.; Mukaiyama, T. *Ibid.* **1977**, 959. (c) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455. (d) Colvin, E. W.; Purcell T. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1718. (e) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693. (f) Corey, E. J.; Brunelle, D. A. *Tetrahedron Lett.* **1976**, 3409. (g) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (h) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875.

(46) While the 4,7-bis((methoxyethoxy)methyl) and 4-(tetrahydropyranyl)-7-((methoxyethoxy)methyl) ether derivatives with the natural C-15 configuration were found to lactonize with this procedure substantially faster than those with the nonnatural configuration,[10a,b] it has been observed[10j] that the 4,7-bis(dioxolan) derivatives lactonize at comparable rates, as in the present case. Although these results are undoubtedly the consequence of subtle differences in nonbonded interactions, an examination of molecular models proves inconclusive, and the exact origin of these differences is obscure. Our finding, independently observed by Winterfeldt and co-workers,[10h] that intramolecular Emmons–Horner cyclization of the *nonnatural* C-15 isomer is considerably faster than of that with the natural configuration (which undergoes resinification on prolonged heating) further complicates any simple explanation. We thank Dr. D. Roland for useful information concerning the intramolecular Emmons–Horner reaction.

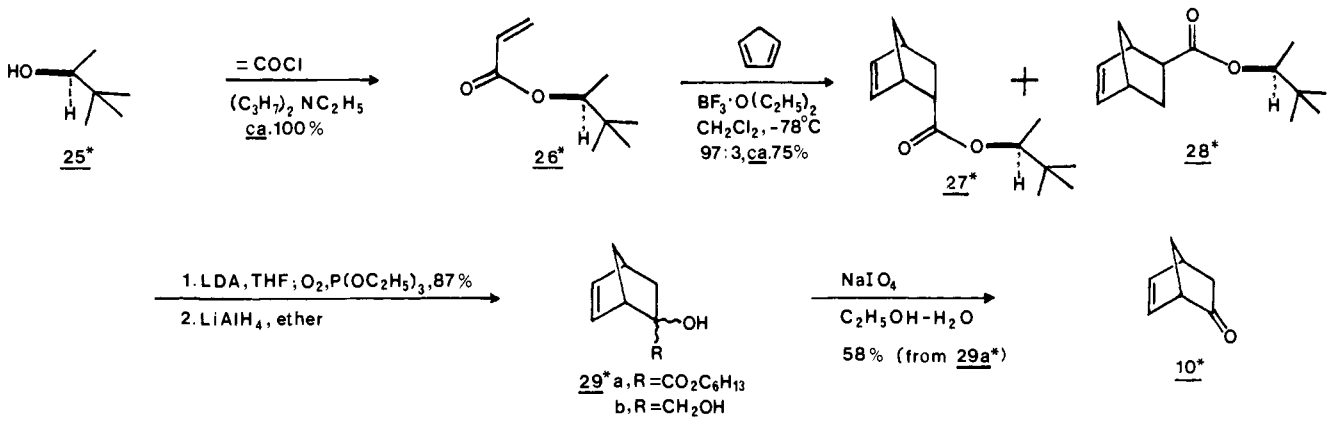
(47) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(48) It is, therefore, undoubtedly safe to conclude that most C-7 protecting groups and not just the previously used acetals[10a,b,e-g] are capable of reversing the stereochemical outcome in the reduction of 4-dehydrobrefeldin-A.[9b]

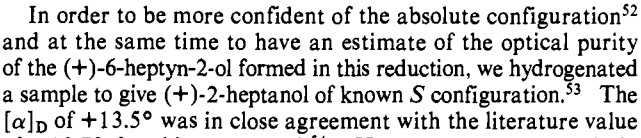
(49) Weisz, I.; Felföldi, K.; Kovacs, K. *Acta Chim. Acad. Sci. Hung.* **1968**, *58*, 189. Yankee, E. W.; Lin, C. H.; Fried, J. *J. Chem. Soc., Chem. Commun.* **1972**, 1120.

(50) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247 and references cited therein. For this particular transformation, this method was distinctly superior to several others, including BCl_3, BBr_3, ethanedithiol with $BF_3{\cdot}OEt_2$ (Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2237. Fujita, E.; Node, M.; Hori, H. *Ibid.* **1977**, 611) or HCl (Grieco, P. A.; Vidari, G.; Ferrino, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, 1619), ethanethiol with various Lewis acids (Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275. See, however: Fuji, K.; Kawabata, T.; Node, M.; Fujita, E. *Tetrahedron Lett.* **1981**, 875. Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662), and Me_3SiI with ZnI_2 (Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, 2305).

Scheme V



In that fermenting yeasts are known to reduce ketones almost invariably to the corresponding secondary alcohols having the *S* configuration (albeit with varying degrees of selectivity),[51] this reduction procedure was examined as a possible direct, enantioselective means of securing the required (*S*)-6-heptyn-2-ol from 6-heptyn-2-one, thereby obviating the need of effecting a resolution. Baker's yeast (*Saccharomyces cerevisiae*) is a particularly convenient organism for carrying out microbial reductions owing not only to its availability and lack of mycelium matter but also to its high general tolerance. Quite pleasingly, this reduction method (with the isolation procedure of Fischer and Wiedemann,[51b] useful for only slightly water soluble but relatively volatile compounds) produced (+)-6-heptyn-2-ol (**18a***)[4] in 56% yield (adjusted for a 40% recovery of starting material) on a 5–10-g scale (eq 5). It was found that optimal reproducible results could be obtained by stopping the reduction after ca. 60% conversion.



In order to be more confident of the absolute configuration[52] and at the same time to have an estimate of the optical purity of the (+)-6-heptyn-2-ol formed in this reduction, we hydrogenated a sample to give (+)-2-heptanol of known *S* configuration.[53] The $[\alpha]_D$ of +13.5° was in close agreement with the literature value of +13.7° for this compound.[54] However, to more precisely determine the optical purity of the (*S*)-(+)-6-heptyn-2-ol, we converted the optically active and racemic acetylenic alcohols to the corresponding Mosher esters with the acid chloride from commercially available (−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid.[55] Although the mixture of diastereomers from the racemic alcohol was inseparable by HPLC and VPC, the ^{19}F NMR spectrum recorded in the presence of $Eu(fod)_3$[15i] displayed two sharp singlets separated by 0.6 ppm. The Mosher ester of (*S*)-(+)-6-heptyn-2-ol under the same conditions exhibited *only* the downfield singlet. The optical purity of the (*S*)-(+)-6-heptyn-2-ol (**18a***) from the microbial reduction could thus be estimated to be *at least* 99%.[56] This material was readily transformed to the stannane **19*** as described for the racemic compound (Scheme IV).

The preparation of (1*S*)-(−)-norbornenone[57] was next undertaken as a means of securing enone **11***, the second chiral component in this convergent synthesis. However, most known approaches to this molecule and to reasonable precursors appeared to be ill-suited for the intended purpose. Resolution[15j,k] of *endo*-norbornenol and *endo*-norbornenecarboxylic acid (as well as of norbornenone itself) and microbial reduction[15m] of norbornenone are not only tedious but also afford the chiral products in only low yield and/or optical purity. Asymmetric induction in the hydroboration of norbornadiene, although attractive because of its directness and the reasonably high optical purity (ca. 50%) of the resultant norbornenol, suffers from an unacceptably low yield (5–15%).[15a–c,k] However, the Diels–Alder reaction between cyclopentadiene and a chiral acrylate, with attendant asymmetric induction, appeared to be a viable means of securing a sufficient amount of (1*S*)-(−)-norbornenone of high optical purity.

Asymmetric induction in the Lewis acid catalyzed Diels-Alder reaction, initially studied in 1963 by Walborsky and co-workers,[15d] has since been reexamined by several different groups.[15e–i] For preparative work in the required optical series, the results taken as a whole suggested that the easily secured[58] (*S*)-(+)-3,3-dimethyl-2-butanol (**25***) would be the most appropriate chiral auxilliary.[15g] Thus, this alcohol, obtained optically pure in 39% yield (78% of theory) on a 0.7-mol scale through resolution of the acid phthalate with brucine followed by saponification,[58] was converted quantitatively to acrylate **26*** (Scheme V). The boron trifluoride etherate catalyzed Diels–Alder reaction between acrylate **26*** and cyclopentadiene (5 equiv) in dichloromethane at −78 °C[15g] afforded a 97:3 mixture of endo and exo esters **27*** and **28***, respectively, in ca. 75% yield. From the work of Sauer and Kredel,[15g] these have principally[59] the 1*S* and 1*R* configurations, respectively.[60]

The conversion of this mixture of esters to norbornenone was effected, with only slight modifications, through a procedure previously described for the transformation of a similar mixture of 8-phenylmenthyl esters to the corresponding norbornenone

(51) (a) For a review, see: Kieslich, K.; "Microbial Transformations of Nonsteroid Cyclic Compounds;" Georg Thieme: Stuttgart, **1976**; pp 16–24. (b) Fischer, F. G.; Wiedemann, O. *Liebigs Ann. Chem.* **1934**, *513*, 260. Fischer, F. G.; Wiedemann, O. *Ibid.* **1935**, *520*, 52. (c) Neuberg, C. *Adv. Carbohydr. Chem.* **1949**, *4*, 75. (d) Schneider, W. P.; Murray, H. C. *J. Org. Chem.* **1973**, *38*, 397. See also references cited.

(52) Dextrorotatory alkyl methyl carbinols generally have the *S* configuration. See: Klyne, W.; Buckingham, J. "Atlas of Stereochemistry"; Chapman and Hall: London, 1974; p 62. Kagan, H. B. "Stereochemistry, Absolute Configurations, One Asymmetric Carbon Atom;" Georg Thieme: Stuttgart, 1977; pp 220–225.

(53) Lukeš, R.; Kovář, J.; Kloubek, J.; Blaha, K. *Collect. Czech. Chem. Commun.* **1960**, *25*, 483 (*Chem. Abstr.* **1960**, *54*, 12180b).

(54) Gil-Av, E.; Charles-Sigler, R.; Fischer, G.; Nurok, D. *J. Gas. Chromatogr.* **1966**, *4*, 51.

(55) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(56) The optical purity of the acetylenic alcohol **18a*** was also directly determined, albeit less precisely, by ^1H NMR with $Eu(hfc)_3$ and found to be in excess of 95%.

(57) That (−)-norbornenone has the 1*S* configuration is known through the correlation of (+)-norbornenone with (+)-norbornanone,[15a] which in turn has been correlated with (−)-fenchone.[15l] The maximum rotation has been calculated to be −1140°[15a] and −1160°.[15b]

(58) Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1911**, *105*, 1120.

(59) The optical purity of the corresponding (purified) *endo*-hydroxymethyl derivative has been reported[15g] to be 88%.[60] Separation and optical enrichment of the endo isomer **27*** (as the free acid) via sequential saponification, iodolactonization (and crystallization), and reduction[15g] could not be performed because of the substantial epimerization that attended the hydrolysis.

(60) Although under similar conditions (+)-8-phenylmenthyl acrylate affords in 59% yield a 92:8 mixture of endo and exo esters with the *purified* *endo*-hydroxymethyl derivative (from the endo ester) having an optical purity of 92%,[15i] the difficult preparation of optically *pure* (+)-8-phenylmenthol[15h] coupled with the higher percentage of the preparatively difficult to separate exo ester (which engenders principally[15g] the antipodal (1*R*)-norbornenone) made the readily available (*S*)-(+)-3,3-dimethyl-2-butanol a much more attractive chiral controlling group.

derivative.[15h] Thus, the ester mixture was converted by sequential α-hydroxylation, reduction (with concomitant recovery of the pure chiral alcohol **25***), and diol cleavage to (1*S*)-(−)-norbornenone (**10***) in 50% overall yield. The optical purity of this product was determined from its optical rotation and from the ^{13}C NMR spectrum of a diastereomeric ketal derivative (formed with (−)-2,3-butanediol[61]) to be, as expected,[15g] 80–85%. The chiral enone **11*** was then readily obtained from **10*** as above in the racemic series (Scheme II, R = *n*-C_4H_9).[62]

With the two chiral conjugate addition partners **11*** and **19*** now available the previous synthesis (Scheme III) was repeated in the natural series, with comparable results throughout. As expected from the optical purity of enone **11***, lactonization of seco acid **23b*** produced the desired optically pure lactone **24a*** (51%) together with a minor amount of a diastereomer (the enantiomer of 15-*epi*-**24a***, 4.5%), readily removed by chromatography. The (+)-brefeldin-A (**1***), mp 204–5 °C, $[\alpha]^{20}_D$ + 93° (authentic sample: mp 204–5 °C, $[\alpha]^{20}_D$ + 93°), so obtained was indistinguishable spectroscopically as well as chromatographically from an authentic sample of the natural product.

In summary, the first *practical* synthesis of natural brefeldin-A, based on an efficient synthesis of the racemic material, has been effected in 12 steps from enone **11*** with an overall yield of 6% (79%/step). The synthesis is particularly well-suited to the preparation for biological screening of diverse chiral analogues of the natural product, a project currently being pursued in our laboratory.

Experimental Section

Solvents were generally redistilled prior to use. Tetrahydrofuran, dimethoxyethane, ether, and hydrocarbons were distilled from sodium hydride–lithium aluminum hydride, toluene and xylene were distilled from sodium, amines were distilled from sodium hydride, dichloromethane and hexamethylphosphoric triamide were distilled from calcium hydride, and acetonitrile was distilled first from phosphorus pentoxide and then from potassium carbonate. Reactions were generally stirred under a nitrogen or argon atmosphere. Reaction products were isolated by addition of water followed by extraction with the solvent indicated, washing with brine, and drying over anhydrous sodium sulfate, magnesium sulfate, or potassium carbonate.

Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70-230 silica gel 60 was employed for dry column chromatography. High-pressure and medium-pressure liquid chromatography separations were effected with Waters Associates and Jobin-Yvon miniprep instruments, respectively. A Beckman Acculab 4 or a Perkin-Elmer Model 397 spectrophotometer was used to record IR spectra (as neat liquid films, unless noted otherwise), and a Beckman DBT spectrophotometer was used for the UV spectra. A JEOL PMX-60 spectrometer was employed for the ^1H NMR spectra (Me_4Si as the internal reference in CCl_4 solutions, except where noted otherwise), and a WP Bruker spectrometer was used for the ^{13}C and ^{19}F NMR spectra. Mass spectra were obtained on a MS-30 AEI mass spectrometer (70 eV, direct insertion probe) or on a VG MICROMASS 70 70F instrument. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Melting points were obtained with a Büchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS, Lyon.

Bicyclo[2.2.1]hept-5-en-2-one (Norbornenone) (10).[14] To a solution of 220 g (2.5 mol) of 2-chloroacrylonitrile in 400 mL of toluene at 70 °C was slowly added 165 g (2.5 mol) of distilled cyclopentadiene. After standing overnight at 45 °C, the solution was distilled to afford 350 g (91%) of 2-chloro-2-cyanobicyclo[2.2.1]hept-5-ene [bp 80–82 °C (20 torr); mp 46 °C]. This material in 2 L of dimethyl sulfoxide was treated with a hot solution of 375 g (6.7 mol) of potassium hydroxide in 125 mL of water. After being stirred for 48 h at room temperature, the solution (containing potassium cyanide) was treated with 2 L of water, and the resultant mixture was distilled. The process was repeated with a second addition of 2 L of water. The distillate was saturated with sodium chloride and then thoroughly extracted with ether, which was processed in the usual manner. Distillation of the residue gave 225 g (91%) of **10**: bp 56 °C (20 torr) [lit.[14] 80–81 °C (45 torr); mp 21–22 °C (lit.[14] 22–23 °C); IR 3070, 1740, 1560 cm^{-1}; ^1H NMR δ 1.7–2.4 (m, 4 H), 2.8–3.3 (m, 2 H), 6.0 (dd, J = 3, 6 Hz, 1 H), 6.4 (dd, J = 3, 6 Hz, 1 H).

***n*-Butyl (4-Oxo-2-cyclopentenyl)acetate (11).** A solution of 21.6 g (0.2 mol) of norbornenone (**10**) in 80 mL of ether was added to 12 g (0.3 mol) of sodium hydroxide dissolved in 70 mL of water.[17] The resultant mixture was rapidly stirred at 10 °C as 22 mL (0.22 mol) of 30% hydrogen peroxide was added over 2 h. After the reaction mixture was stirred for an additional 1 h at room temperature, the aqueous phase was separated, washed with 80 mL of ether, and then concentrated under reduced pressure. The oily residue (**14a**) was stirred with 90 mL (0.8 mol) of 1-iodobutane in 600 mL of hexamethylphosphoric triamide overnight,[20] and the resultant crude allylic alcohol ester **14c** (R = C_4H_9) was then isolated with ether in the usual fashion. The crude product was stirred with 3 g of activated charcoal in 1.5 L of chloroform for 15 min. The mixture was filtered and the filtrate was treated with 350 g of activated manganese dioxide and then stirred vigorously for 36 h, after which an additional 150 g of manganese dioxide was added followed by stirring for 24 h. After filtration, concentration of the chloroform solution and silica gel chromatography of the crude product with 22% ethyl acetate in hexane yielded 27.6 g (70%) of **11**: IR 1735, 1715, 1590 cm^{-1}; ^1H NMR δ 0.8–2.8 (m, 11 H), 3.0–3.4 (m, 1 H), 4.0 (t, J = 6 Hz, 2 H), 5.85 (dd, J = 3, 6 Hz, 1 H), 7.4 (dd, J = 2, 6 Hz, 1 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H 8.22. Found: C, 67.14; H, 8.40.

Latter fractions yielded 1.9 g (8%) of 2-oxabicyclo[3.3.0]oct-7-en-3-one[16] (**13**): IR 3060, 1725, 1710 cm^{-1}; ^1H NMR δ 1.8–3.3 (m, 5 H), 5.3 (m, 1 H), 5.9 (m, 2 H).

2,3-Epoxy-3-methylcyclohexanone (16).[21,22] To a solution of 66 g (0.6 mol) of 3-methyl-2-cyclohexenone (**15**) in 600 mL of methanol at 10 °C was added over 10 min 183 mL (1.8 mol) of 30% hydrogen peroxide followed by the dropwise addition of 4 mL (0.02 mol) of 5 N sodium hydroxide. After being stirred at 10 °C for an additional 2.5 h, the reaction mixture was poured into cold brine. The crude product was isolated with dichloromethane in the usual manner and then distilled to give 68 g (90%) of **16**: bp 91 °C (20 torr); IR 1705, 1255, 810, 770 cm^{-1}; ^1H NMR δ 1.45 (s, 3 H), 1.6–2.6 (m, 6 H), 3.05 (s, 1 H).

6-Heptyn-2-one (17).[21,22] A 19-g (0.15 mol) sample of epoxide **16** in 300 mL of dichloromethane and 150 mL of acetic acid at −30 °C was treated with 28.2 g (0.16 mol) of *p*-toluenesulfonylhydrazine also in 300 mL of dichloromethane and 150 mL of acetic acid at −30 °C, and the resultant mixture was then stirred at −15 °C for 17 h, 0 °C for 4.5 h, and room temperature for 4 h. The crude product was isolated with ether and then purified over silica gel with 11% ether in pentane to give 9.4 g (57%) of **17**: IR 3290, 2120, 1720 cm^{-1}; ^1H NMR δ 1.8 (t, J = 2.5 Hz, 1 H), 2.1 (s, 3 H), 1.2–2.3 (m, 4 H), 2.5 (t, J = 6.5 Hz, 2 H).

Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.12; H, 9.10.

6-Heptyn-2-ol (18a).[63] A solution of 9.0 g (82 mmol) of ketone **17** in 20 mL of ether was added over 5 min to a stirred suspension of 1.6 g (42 mmol) of lithium aluminum hydride in 200 mL of ether at 0 °C. After 15 min, the excess hydride was destroyed by careful addition of water, and the resultant mixture was filtered. The crude product was isolated in the usual manner to yield 8.9 g (97%) of alcohol **18a**: IR 3340, 3300, 2120 cm^{-1}; ^1H NMR δ 1.1 (d, J = 6 Hz, 3 H), 1.3–1.7 (m, 4 H), 1.75 (t, J = 2.5 Hz, 1 H), 2–2.3 (m, 2 H), 2.7 (s, 1 H), 3.45–3.9 (m, 1 H).

6-((*tert*-Butyldimethylsilyl)oxy)-1-heptyne (18b). A solution of 12 g (0.11 mol) of alcohol **18a** and 7.6 g (0.12 mol) of imidazole in 50 mL of dimethylformamide was treated under nitrogen with stirring with 16.8 g (0.11 mol) of *tert*-butyldimethylchlorosilane.[23] After being stirred for 2.5 h at 35 °C, the reaction mixture was poured into water, and the crude product was isolated with pentane and purified by silica gel chromatography with 1.5% ether in pentane to afford 21.6 g (89%) of **18b**: IR 3370, 2120, 1260, 840, 780 cm^{-1}; ^1H NMR δ 0.8 (s, 9 H), 1.05 (d, J = 6 Hz, 3 H), 1.3–1.6 (m, 4 H), 1.7 (t, J = 2.5 Hz, 1 H), 1.9–2.2 (m, 2 H), 3.5–3.9 (m, 1 H).

Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 68.70; H, 11.56.

6-((*tert*-Butyldimethylsilyl)oxy)-1-(tri-*n*-butyl)stannyl-1-heptene (19). A 13.2-g (58 mmol) sample of acetylene **18b** was heated at 95 °C with 17.7 g (61 mmol) of tributyltin hydride and 80 mg of azobis(isobutyronitrile) (AIBN) for 2 h.[24] An additional 100 mg of tributyltin hydride

(61) G. Gagnaire, unpublished results. We thank G. Gagnaire for carrying out this determination.

(62) The optical rotation of the corresponding chiral dihydro keto acid, obtained from **11*** conventionally, indicated an optical purity of ca. 85% based on several literature values, in accord with the above range. See: Hill, R. K.; Edwards, A. G. *Tetrahedron* **1965**, *21*, 1501 and references cited therein. Kuritani, H.; Takaoka, Y.; Shingu, K. *J. Org. Chem.* **1979**, *44*, 452. This optical purity is also in accord with the results of Sauer and Kredel.[15g,59] To our knowledge this is the highest optical purity obtained to date for (−)-norbornenone.

(63) Peterson, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521.

and 20 mg of AIBN were then added, and the mixture was heated for 3 h at 100 °C, after which another 30 mg of tributyltin hydride and 15 mg of AIBN were added followed by heating at 130 °C for 2 h. Direct distillation afforded 29.5 g (98%) of **19**: bp 130–140 °C (0.02 torr), IR 1600, 1260, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.1 (d, J = 7 Hz, 3 H), 0.7–2.2 (m, 33 H), 3.7–3.9 (m, 1 H), 5.85–6.0 (m, 2 H); ^{13}C NMR (neat, Me_4Si) δ 149.6 and 149.1 (C-2), 127.2 and 127.8 (C-1). Peak ratios were 85:15.

***n*-Butyl ([1*R**,2*S**]-2-[(1*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-heptenyl]-4-oxocyclopentyl)acetate (20).** A 29-g (56 mmol) sample of stannane **19** was added to *n*-butyllithium (48 mmol) in 60 mL of tetrahydrofuran at −78 °C.[25] The solution was allowed to warm to 0 °C and was stirred for 50 min at this temperature. After being recooled to −100 °C, this solution was added to a solution of 7.3 g (56 mmol) of pentynylcopper[26] and 20.5 mL (112 mmol) of tris(dimethylamino)phosphine in 80 mL of tetrahydrofuran, also at −100 °C. After being stirred for 1.5 h at ca. −90 °C, the resultant cuprate **3** was treated at −100 °C with 9.2 g (47 mmol) of enone ester **11** in 12 mL of tetrahydrofuran. The reaction mixture was stirred for 2 h at −90 to −80°C, and then a saturated aqueous ammonium chloride solution (30 mL) was added, and the resultant mixture was poured into ether–aqueous ammonium chloride containing a few drops of ammonium hydroxide. After this mixture was stirred for 1 h, the crude product was isolated with ether in the usual manner and was purified by silica gel chromatography with 14% ether in pentane to produce 11.9 g (60%) of **20**: IR 1750–1740, 1260, 970, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1–2.7 (m, 21 H), 3.5–3.8 (m, 1 H), 3.9 (t, J = 6 Hz, 2 H), 5.2–5.4 (m, 2 H).

Anal. Calcd for $C_{24}H_{44}O_4Si$: C, 67.86; H, 10.44. Found: C, 67.78; H, 10.46.

The slightly less polar corresponding 5,9-cis isomer was also isolated (600 mg, 3%): IR 1740, 1260, 970, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1–2.7 (m, 21 H), 3.5–3.8 (m, 1 H), 3.9 (t, J = 6 Hz, 2 H), 5.2–5.4 (m, 2 H).

Anal. Calcd for $C_{24}H_{44}O_4Si$: M_r 424.3008. Found: M_r (mass spectrum) 424.2996.

This material and **20** were separately hydrogenated (10% palladium on charcoal, ethyl acetate) and afforded distinctly different products.

***n*-Butyl ([1*R**,2*S**,4*S**]-2-[(1*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-heptenyl]-4-hydroxycyclopentyl)acetate (21a).** To a solution of 10.8 g (25.5 mmol) of ketone **20** in 300 mL of tetrahydrofuran at −95 °C under nitrogen was added 35 mL (28 mmol) of a 0.8 M solution of L-Selectride[30] in tetrahydrofuran. After being stirred for 1 h at −90 °C, the solution was treated simultaneously with 10 mL (30 mmol) of 3 N sodium hydroxide and 10 mL (95 mmol) of 30% hydrogen peroxide. The reaction mixture was stirred for 5 min without the cooling bath and then poured into ether–brine. The crude product was isolated with ether in the usual fashion and purified by silica gel chromatography with 38% ether in pentane to afford 10.5 g (97%) of a mixture of the α-alcohol **21a** and the corresponding β alcohol.

A 5.0-g sample of this epimeric mixture of alcohols in 800 mL of toluene containing 34 mg of *p*-toluenesulfonic acid was refluxed for 8 h, with the removal of 15 mL of distillate each hour. The crude product was isolated in the normal manner and then purified by silica gel chromatography with ether in pentane to give 1.03 g (25%) of lactone **7**: IR 1740, 1260, 975, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1.2–2.7 (m, 14 H), 3.5–3.8 (m, 1 H), 4.5–4.7 (m, 1 H), 5.1–5.3 (m, 2 H).

Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 68.00; H, 10.42.

Further elution provided 3.35 g (67%) of alcohol **21a**: IR 3420, 1735, 1260, 975, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1–2.4 (m, 21 H), 3.5–4.2 (m, 2 H), 3.8 (t, J = 7 Hz, 2 H), 5–5.2 (m, 2 H).

Anal. Calcd for $C_{24}H_{46}O_4Si$: C, 67.55; H, 10.87. Found: C, 67.71; H, 10.77.

***n*-Butyl ([1*R**,2*S**,4*S**]-2-[(1*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)acetate (21b).** A 4.8-g (11.2 mmol) sample of alcohol **21a** in 20 mL of acetonitrile and 10 mL (161 mmol) of methyl iodide was treated with 4.1 g (18 mmol) of silver oxide, and the mixture was then refluxed for 12 h.[33] A second addition [1.4 g (6 mmol) of silver oxide and 3 mL (50 mmol) of methyl iodide, reflux for 24 h] and then a third addition [1.4 g (6 mmol) of silver oxide and 3 mL (50 mmol) of methyl iodide, reflux for 10 h] were followed by dilution of the reaction mixture with ether and filtration through Celite. The crude product was isolated with ether and then purified by silica gel chromatography with ether in pentane to give 3.86 g (78%) of **21b**, followed by 0.77 g (16%) of starting material **21a**. Ether **21b**: IR 1735, 1255, 975, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1–2.4 (m, 21 H), 3.0 (s, 3 H), 3.4–3.8 (m, 2 H), 3.9 (t, J = 7 Hz, 2 H), 5.05–5.3 (m, 2 H).

Anal. Calcd for $C_{25}H_{48}O_4Si$: C, 68.13; H, 10.98. Found: C, 68.23; H, 10.88.

***n*-Butyl 2,2-Bis(methylthio)([1*R**,2*S**,4*S**]-2-[(1*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)acetate (22a).** A solution of 3.44 g (7.8 mmol) of ether **21b** in 40 mL of tetrahydrofuran under nitrogen was treated successively as follows: at −78 °C with 8.1 mL (8.6 mmol) of a 1.06 M tetrahydrofuran solution of lithium diisopropylamide, followed by stirring at −78 °C for 20 min; at −78 °C with 890 μL (9.4 mmol) of methyl methanethiosulfonate,[40] followed by warming to room temperature, stirring for 20 min, and recooling to −78 °C; at −78 °C with 9.6 mL (10.2 mmol) of a 1.06 M tetrahydrofuran solution of lithium diisopropylamide, followed by warming to 0 °C, stirring for 20 min, and then recooling to −78 °C; at −78 °C with 1.03 mL (10.96 mmol) of methyl methanethiosulfonate, followed by warming to room temperature and stirring for 15 min. A saturated aqueous solution of ammonium chloride was then added to the solution, and the crude product was isolated with ether and purified by silica gel chromatography with 8% ether in pentane to provide 3.95 g (95%) of **22a**: IR 1725, 1250, 970, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 0.9–2.8 (m, 19 H), 2.0 (s, 6 H), 3.1 (s, 3 H), 3.4–3.7 (m, 2 H), 3.95 (t, J = 7 Hz, 2 H), 5.1–5.3 (m, 2 H).

Anal. Calcd for $C_{27}H_{52}O_4S_2Si$: C, 60.85; H, 9.84. Found: C, 60.56; H, 9.88.

2,2-Bis(methylthio)([1*R,2*S**,4*S**]-2-[(1*E*)-6-((*tert*-butyldtmethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)ethanal (22b).** A 2.07-g (3.89 mmol) sample of ester **22a** in 40 mL of toluene at −110 °C (ether–liquid nitrogen bath) under nitrogen was treated with 6.5 mL (7.8 mmol) of a 1.2 M toluene solution of diisobutylaluminum hydride, and the mixture was then stirred vigorously for 2.5 h at −110 to −100 °C. Following the addition of 2 mL of methanol at this temperature and 5 mL of saturated aqueous ammonium chloride at room temperature, the mixture was poured into 100 mL of ether–20 mL of saturated aqueous ammonium chloride. The pH was adjusted to 4 with aqueous hydrochloric acid, and the mixture was stirred for 30 min. The crude product was then isolated with ether and purified over silica gel with 9% ether in pentane to give 1.46 g (82%) of **22b**: IR 2720, 1710, 1260, 975, 840, 780 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1–2.8 (m, 12 H), 1.92 (s, 3 H), 1.98 (s, 3 H), 3.1 (s, 3 H), 3.5–3.8 (m, 2 H), 5.1–5.3 (m, 2 H), 8.75 (s, 1 H).

Anal. Calcd for $C_{23}H_{44}O_3S_2Si$: C, 59.94; H, 9.62. Found: C, 60.20; H, 9.59.

Elution with ether of the material remaining on the column gave 80 mg, composed mostly of the corresponding alcohol. Oxidation of this material with 1.0 g of Collins reagent in 10 mL of dichloromethane followed by purification of the resultant crude product gave an additional 37 mg (2%) of aldehyde **22b**.

(2*E*)-Ethyl 4,4-Bis(methylthio)-4-([1*R,2*S**,4*S**]-2-[(1*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)-2-butenoate (22c).** Ethyl (trimethylsilyl)acetate (490 μL, 2.7 mmol) was added to 12.9 mL (2.45 mmol) of a 0.19 M tetrahydrofuran solution of lithium diisopropylamide at −80 °C under nitrogen.[43] After being stirred for 15 min at −80 °C, the solution was treated with 1.04 g (2.26 mmol) of aldehyde **22b** in 8 mL of tetrahydrofuran. The solution was allowed to warm to −35 °C over several hours and then left at −35 °C overnight. At −10 °C, the solution was treated with 3 mL of saturated aqueous ammonium chloride, and the product was then isolated with ether in the usual manner and purified over silica gel with 8% ether in pentane to afford 1.03 g (86%) of **22c**: IR 1720, 1635, 1255, 975, 835, 775 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 1.05 (d, J = 7 Hz, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.0–2.6 (m, 12 H), 1.90 (s, 3 H), 1.93 (s, 3 H), 3.1 (s, 3 H), 3.5–3.7 (m, 2 H), 4.1 (q, J = 7 Hz, 2 H), 5.15–5.4 (m, 2 H), 6.2 (AB q, J = 16 Hz, $\delta_a - \delta_b$ = 53 Hz, 2 H).

(2*E*)-Ethyl 4,4-Bis(methylthio)-4-([1*R,2*S**,4*S**]-2-[(1*E*)-6-hydroxy-1-heptenyl]-4-methoxycyclopentyl)-2-butenoate (23a).** A 990-mg (1.87 mmol) sample of silyl ether **22c** in 20 mL of 3:1 acetic acid–water was left for 4 h at room temperature and then poured into 200 mL of ether and 50 mL of water containing 40 g of potassium carbonate. The crude product was isolated with ether and was purified by silica gel chromatography with 45% ether in pentane to give 750 mg (97%) of **23a**: IR 3440, 1715, 1635, 975 cm^{-1}; ^1H NMR δ 1.1 (d, J = 7 Hz, 3 H), 1.3 (t, J = 7 Hz, 3 H), 1.1–2.7 (m, 13 H), 1.95 (s, 3 H), 1.98 (s, 3 H), 3.16 (s, 3 H), 3.6–3.9 (m, 2 H), 4.06 (q, J = 7 Hz, 2 H), 5.2–5.4 (m, 2 H), 6.2 (AB q, J = 15 Hz, $\delta_a - \delta_b$ = 53 Hz, 2 H).

Anal. Calcd for $C_{21}H_{36}O_4S_2$: C, 60.54; H, 8.71. Found: C, 60.52; H, 8.47.

(2*E*)-4,4-Bis(methylthio)-4-([1*R,2*S**,4*S**]-2-[(1*E*)-6-hydroxy-1-heptenyl]-4-methoxycyclopentyl)-2-butenoic Acid (23b).** A 670-mg (1.6 mmol) sample of ester **23a** in 25 mL of methanol and 8 mL of water containing 600 mg (14 mmol) of lithium hydroxide monohydrate was stirred for 18 h at 30 °C. Conventional treatment of the reaction mixture

provided 605 mg (97%) of **23b**: IR 3400, 1705, 1635, 975 cm^{-1}; ^1H NMR δ 1.15 (d, J = 7 Hz, 3 H), 1.90 (s, 3 H), 1.96 (s, 3 H), 1–2.9 (m, 12 H), 3.1 (s, 3 H), 3.6–3.9 (m, 2 H), 5.1–5.4 (m, 2 H), 6.25 (AB q, J = 15 Hz, $\delta_a - \delta_b$ = 56 Hz, 2 H), 7.6 (br s, 2 H).

(2*E*,6*R,10*E*,11a*R**,13*R**,14a*S**)-1,1-Bis(methylthio)-1,6,7,8,9,11a,12,13,14,14a-decahydro-13-methoxy-6-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-4-one (24a).** The 2-pyridinethiol ester of **23b** was prepared by treating 552 mg (1.42 mmol) of acid alcohol **23b** in 10 mL of dichloromethane at 0 °C under nitrogen with 252 μL (1.8 mmol) of triethylamine followed by 8 mL (ca. 1.6 mmol) of an ca. 0.2 M dichloromethane solution of 2-thiopyridyl chloroformate.[45b] After the reaction mixture was stirred for 1.5 h, an additional 65 μL (0.45 mmol) of triethylamine and 2 mL (ca. 0.4 mmol) of the ca. 0.2 M solution of 2-thiopyridyl chloroformate were added, and stirring was continued for 0.5 h. The crude 2-pyridinethiol ester, isolated with dichloromethane, was dissolved in 20 mL of xylene, which was then removed under reduced pressure.

The above 2-pyridinethiol ester of **23b** was dissolved in 30 mL of xylene, 10 mL of which was added over 9 h via a syringe pump to 200 mL of xylene refluxing under nitrogen.[45g] After the completion of the addition, the solution was refluxed for an additional 2 h. The remaining material was similarly transformed in two equal batches. The three reaction mixtures were combined and freed of solvent under reduced pressure. Purification of the residue on silica gel with 15% ether in pentane afforded 175 mg (33%) of **24a**: R_f 0.38 (SiO_2, 30% ether–pentane); IR 1715, 1630, 970 cm^{-1}; ^1H NMR δ 1.25 (d, J = 6 Hz, 3 H), 1.93 (s, 3 H), 1.97 (s, 3 H), 1–3 (m, 12 H), 3.15 (s, 3 H), 3.6 (quint, J = 5 Hz, 1 H), 4.57 (m, 1 H), 4.95–5.85 (m, 2 H), 6.25 (AB q, J = 15 Hz, $\delta_a - \delta_b$ = 78.6 Hz, 2 H).

Anal. Calcd for $C_{19}H_{30}O_3S_2$: C, 61.58, H, 8.16. Found: C, 61.64; H, 8.25.

Also isolated was 189 mg (35%) of the 6*S** (or 15-epi) isomer: R_f 0.48 (30% ether–pentane); IR 1715, 1630, 970 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3 H), 1.83 (s, 3 H), 2.11 (s, 3 H), 1.0–2.5 (m, 12 H), 3.15 (s, 3 H), 3.65 (quint, J = 5 Hz, 1 H), 4.9 (m, 1 H), 5–5.26 (m, 2 H), 6.13 (AB q, J = 15 Hz, $\delta_a - \delta_b$ = 56 Hz, 2 H).

Anal. Calcd for $C_{19}H_{30}O_3S_2$: C, 61.58; H, 8.16. Found: C, 61.55; H, 8.16.

(2*E*,6*R,10*E*,11a*R**,13*R**,14a*S**)-13-Methoxy-6-methyl-7,8,9,11a,12,13,14,14a-octahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-(6*H*)-dione (24b).** A solution of 166 mg (0.46 mmol) of thioketal **24a** in 3 mL of acetonitrile was added to a solution of 246 mg (1.84 mmol) of *N*-chlorosuccinimide and 352 mg (2.07 mmol) of silver nitrate in 12 mL of 3:1 acetonitrile–water at −5 °C protected from light.[47] The resultant mixture was stirred for 0.5 h at −5 °C and 0.5 h at room temperature and was then poured into 20 mL of ether and 5 mL of a saturated aqueous solution of sodium sulfite. The crude product was isolated with ether and then rapidly filtered over a small quantity of silica gel with 30% ether in pentane to afford 94 mg (72%) of **24b** as a relatively unstable oil: R_f 0.30 (30% ether–pentane); IR 3040, 1725, 1695, 1630, 970 cm^{-1}; ^1H NMR δ 1.28 (d, J = 6 Hz, 3 H), 1–1.3 (m, 12 H), 3.15 (s, 3 H), 3.6 (quint, J = 5 Hz, 1 H), 4.45 (m, 1 H), 5.05–5.7 (m, 2 H), 6.8 (AB q, J = 16 Hz, $\delta_a - \delta_b$ = 80 Hz, 2 H).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.40; H, 8.19.

The same reaction conditions with 15 mg of the 6*S** (or 15-epi) isomeric thioketal produced 10 mg (84%) of the corresponding isomer of **24b**: R_f 0.37 (30% ether–pentane); IR 3040, 1720, 1700, 1630, 975 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3 H), 1–3 (m, 12 H), 3.13 (s, 3 H), 3.75 (m, 1 H), 5.0 (m, 1 H), 5.2–5.45 (m, 2 H), 6.56 (AB q, J = 15 Hz, $\delta_a - \delta_b$ = 57 Hz, 2 H).

(1*R,2*E*,6*S**,10*E*,11a*S**,13*S**,14a*R**)-1,6,7,8,9,11a,12,13,14,14a-Decahydro-1-hydroxy-13-methoxy-6-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-4-one (24c).** A 91-mg (0.32 mmol) sample of ketone **24b** in 3.5 mL of methanol at −110 °C was treated with 16 mg (0.42 mmol) of sodium borohydride and then left for 1 h at −78 °C. Acetone (100 μL) was then added, and the reaction mixture was allowed to warm to room temperature. The crude product was isolated with ethyl acetate and then purified over silica gel with 2% methanol in methylene chloride to give 78 mg (85%) of **24c**: mp 90.5–91 °C (ether–pentane); IR 3450, 1710, 1690, 1640 cm^{-1}; ^1H NMR δ 1.22 (d, J = 7 Hz, 3 H), 1.1–2.5 (m, 13 H), 3.15 (s, 3 H), 3.6 (quint, J = 5 Hz, 1 H), 3.82 (m, 1 H), 4.4–5 (m, 1 H), 5.05–5.8 (m, 2 H), 5.63 (dd, J = 1.5, 15 Hz, 1 H), 7.05 (dd, J = 3.5, 15 Hz, 1 H).

(1*R,2*E*,6*S**,10*E*,11a*S**,13*S**,14a*R**)-1,6,7,8,9,11a,12,13,14,14a-Decahydro-1,13-dihydroxy-6-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-4-one [(±)-Brefeldin-A] (1).** A 15-mg (0.05 mmol) sample of methyl ether **24c** in 1 mL of acetonitrile was treated with 150 μL of a 20% solution of (*N*-trimethylsilyl)diethylamine in pentane and then left for 15 h at room temperature.[49] Removal of volatiles under reduced pressure left the crude silyl ether of **24c**. This residue was dissolved in 1 mL of dry acetonitrile and was treated, protected from light at room temperature under argon, with 45 mg (0.3 mmol) of dry sodium iodide and 39 μL (0.3 mmol) of chlorotrimethylsilane.[50] After the reaction mixture was stirred for 50 min, an additional 30 mg (0.2 mmol) of sodium iodide and 26 μL (0.2 mmol) of chlorotrimethylsilane were added, and stirring was continued for 1 h, followed by another addition of 15 mg (0.1 mmol) of sodium iodide and 13 μL (0.1 mmol) of chlorotrimethylsilane. After 40 min, 1 mL of water and 5 mL of ethyl acetate were added. The mixture was extracted with ethyl acetate, which was washed with sodium thiosulfate and brine and dried over magnesium sulfate. Removal of the solvent and rapid filtration of the residue over a small amount of silica gel with 50% methanol in methylene chloride afforded a mixture of **24c** and **1**. Separation of this mixture was carried out by HPLC (Whatman Partisil M9 10/50 ODS2, 80% methanol–20% water; retention times: **1**, 12 min; **24c**, 18 min at 3 mL/min) to afford 5.2 mg (35%) of starting material **24c** and 6.5 mg (45%, or 69% based on consumed **24c**) of (±)-brefeldin-A (**1**): mp 177–177.5 °C (ethyl acetate) (lit.[10c] mp 175–175.5 °C); IR (KBr) 3350, 1705, 1640, 1240, 1000, 980, 970 cm^{-1}; ^1H NMR (CD_3OD) δ 1.3 (d, J = 6 Hz, 3 H), 0.7–2.5 (m, 12 H), 3.9 (m, 1 H), 4.08 (quint, J = 5 Hz, 1 H), 4.65 (m, 1 H), 4.8–5.8 (m, 2 H), 5.6 (dd, J = 2, 15 Hz, 1 H), 7.2 (dd, J = 3, 15 Hz, 1 H); mass spectrum, m/e 280 (M^+). These spectra were identical with those of an authentic sample of natural brefeldin-A. Furthermore, an admixture of **1** and the natural product was chromatographically (TLC, HPLC) inseparable.

(*S*)-(+)-3,3-Dimethyl-2-butanol (25*)[4]. This compound was secured as described by Pickard and Kenyon,[58] except that the mother liquors from the recrystallizations of the brucine salt of the acid phthalate were also subjected to a series of recrystallizations (thereby raising the overall yield of **25*** from **25** to 39%, or 78% of theory). Alcohol **25***: $[\alpha]^{20}_D$ +8.04° (neat) (lit.[64] highest value +8.2°).

(1*S*,4*S*)-(−)-Bicyclo[2.2.1]hept-5-en-2-one (Norbornenone) (10*). A 35-g (0.34 mol) sample of alcohol **25*** in 200 mL of dichloromethane and 71 mL (0.41 mol) of *N*-ethyldiisopropylamine at −40 °C was treated slowly with 31 mL (0.37 mol) of acryloyl chloride. After 10 min, the crude product was isolated with ether and then partially dissolved in pentane. Filtration and evaporation of the pentane left 56 g of crude acrylate **26***, a small sample of which was distilled for characterization: IR 1725, 1640, 1620, 980, 810 cm^{-1}; ^1H NMR δ 0.91 (s, 9 H), 1.13 (d, J = 6 Hz, 3 H), 4.56 (q, J = 6 Hz, 1 H), 5.4–6.4 (m, 2 H); $[\alpha]^{20}_D$ +33.3° (neat), +39.0° (*c* 2, chloroform).

Acrylate **26*** (56 g, 0.34 mol) in 210 mL of dichloromethane at −78 °C was treated with 45 mL (0.36 mol) of boron trifluoride etherate over 10 min, followed by 120 mL (1.41 mol) of cyclopentadiene in 10-mL portions over 3 h.[15g] After an additional 30 min, some starting material **26*** remained (VPC), and therefore an additional 20 mL of cyclopentadiene was added to the reaction mixture. After being stirred for another 15 min, the reaction mixture was poured into 700 mL of chloroform and 170 mL of aqueous sodium bicarbonate. The organic phase was washed with aqueous sodium bicarbonate and dried and the solution was filtered. The addition of 500 mL of ether to this solution caused a copious precipitation of polymeric material, which was removed by filtration. Evaporation of the solvents yielded an oil, which was dissolved in 200 mL of ether. The addition of 700 mL of pentane effected a second precipitation. The precipitate was filtered off and washed with pentane. Evaporation of the solvent left an oil, which was partially dissolved in 1 L of methanol. The insoluble material was filtered off and washed with additional methanol and the filtrates were concentrated to yield 57 g of crude product. Analysis of the product by VPC (10% carbowax, 2 m) indicated only two peaks corresponding to the endo ester (97%) and exo ester (3%): IR 3040, 1735, 715 cm^{-1}; ^1H NMR δ 0.91 (s, 9 H), 1.05 (d, J = 6 Hz, 3 H), 1.2–2 (m, 4 H), 2.6–3.2 (m, 3 H), 4.4 (q, J = 6 Hz, 1 H), 5.58–5.8 (m, 1 H), 5.87–6.06 (m, 1 H); $[\alpha]^{20}_D$ −67° (*c* 5, chloroform).

A 56-g (ca. 0.25 mol) sample of the above mixture, composed principally of esters **27*** and **28***, in 200 mL of tetrahydrofuran at −78 °C under nitrogen was treated with 190 mL (0.33 mol) of a 1.75 M solution of lithium diisopropylamine in tetrahydrofuran. The solution was allowed to warm to −15 °C, stirred for 3 h at this temperature, recooled to −78 °C, and then added over 20 min to a solution at −78 °C of 88 mL (0.5 mol) of triethyl phosphite in 400 mL of tetrahydrofuran through which dry oxygen was bubbled.[15h] After an additional 0.5 h, the crude product was isolated with ether. Following the removal of the excess triethyl phosphite under reduced pressure (0.01 torr, 40 °C), the product was purified over silica gel with 15% ether in pentane to give 52 g (87%), composed mainly of the hydroxy ester isomers **29a***: IR 3480, 3070, 1720–1700, 705 cm^{-1}; ^1H NMR δ 0.9 (s, 9 H), 1.1 (d, J = 6 Hz, 3 H),

(64) Newman, P.; Rutkin, P.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 465.

1.2–3.2 (m, 7 H), 4.5 (q, J = 6 Hz, 1 H), 5.58–5.8 (m, 1 H), 5.93–6.1 (m, 1 H).

A 40-g (0.17 mol) sample of the above hydroxy ester mixture **29a*** was added dropwise to a stirred suspension of 5 g (0.13 mol) of lithium aluminum hydride in 350 mL of ether at −25 °C. After being stirred for an additional 0.5 h at −25 °C and 2 h at 0 °C, the mixture was treated dropwise with a saturated solution of sodium potassium tartrate. Thorough extraction of the mixture with ether followed by drying and careful concentration of the ether yielded a mixture of alcohol **25*** and diols, principally isomers **29b***. The alcohol **25*** (13 g, 48% recovery from **26***) was separated from the mixture by evaporative distillation (0.2 torr, 40 °C, 30–40 h) into a cold trap and was purified by redistillation at atmospheric pressure from a small amount of calcium hydride (bp 117–119 °C). The residue (28 g) from the evaporative distillation consisted mainly of the diols **29b***: IR 3390, 3060, 705 cm^{-1}.

The above 28-g (0.16 mol) sample of diols **29b*** in 20 mL of ethanol was added to a solution at 0 °C of 35 g (0.16 mol) of sodium periodate in 195 mL of water to which disodium hydrogen phosphate had been added to effect pH 7.5. After the addition, the mixture was stirred for 2 h at room temperature, treated with an additional 5 g of sodium periodate in 30 mL of water, and then stirred for another 30 min. The reaction mixture was saturated with sodium chloride and then thoroughly extracted with ether. After being washed with brine, the organic phase was dried and carefully concentrated to 60 mL. Analysis of this solution by VPC indicated that it contained 10.5 g (58% from **29a***) of norbornenone (**10***). A comparable sample purified by silica gel chromatography with 10% ether in pentane followed by distillation had IR and ^1H NMR spectra identical with those of the previously obtained racemic norbornenone (**10**); $[\alpha]^{20}_D$ = −920° (*c* 0.3, isooctane).[57]

(+)-*n*-Butyl ([1*S*]-4-Oxo-2-cyclopentenyl)acetate (11*). The above 60-mL ether solution of **10*** (0.1 mol) was treated with 50 mL of water containing 8 g (0.2 mol) of sodium hydroxide and then, with efficient stirring at 10 °C, with 11 mL of 30% hydrogen peroxide over 2 h.[17] After an additional 15 min, the ether phase was separated, and the aqueous phase, after being washed with ether, was concentrated. The resultant oil was treated with 60 mL (0.52 mol) of 1-iodobutane in 300 mL of hexamethylphosphoric triamide.[20] Completion of the transformation as described above for **11** yielded 10.1 g (53%) of **11*** having IR and ^1H NMR spectra identical with those of the previously obtained racemic material **11**; $[\alpha]^{20}_D$ +89° (*c*, 3, dichloromethane).

(*S*)-(+)-6-Heptyn-2-ol (18a*). Baker's yeast (280 g) was added to a rapidly stirred solution (1 L) of 70 g of sucrose and 50 g of sodium dihydrogen phosphate in water. When the rate of fermentation became constant (as measured by the evolution of carbon dioxide through a bubbler), the suspension was warmed to 34 °C with a thermostatically heated water bath. After 2 h of fermentation, 7 g (63.6 mmol) of 6-heptyn-2-one (**17**) in 400 mL of 15% aqueous sucrose solution was added over 4 h. Sucrose (as a powder or 30% aqueous solution, ca. 100 g over each 24-h period) and fresh fermenting baker's yeast (after each 48–72-h period) were then added periodically to the mixture in order to maintain a useful rate of fermentation. After 8 days, 1.8 L was distilled from the mixture, water (3 L) was added to the residue, and an additional 1.5 L of distillate was collected. After saturation of the distillate with sodium chloride, the mixture was thoroughly extracted with ether, the ether and ethanol were carefully removed by distillation, and the residue was purified over silica gel with ether in pentane to give 2.8 g (40%) of **17** and 2.4 g (34%, or 56% based on consumed **17**) of **18a***. The IR and ^1H NMR spectra of **18a*** and **18a** were indistinguishable. A sample of **18a***, purified by preparative VPC (glass column, 5% SE-30), had $[\alpha]^{20}_D$ +14.7° (*c* 10, benzene). Hydrogenation (5% palladium on charcoal, ethyl acetate) of a small amount of **18a*** and purification of the product by preparative VPC followed by distillation gave 2-heptanol having $[\alpha]^{20}_D$ +13.5° (*c* 3, benzene) (lit.[54] $[\alpha]_D$ +13.7°).

Samples of **18a** and **18a*** were individually esterified in carbon tetrachloride–pyridine with the acid chloride from (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid[55] (Fluka). The ^{19}F NMR spectrum (recorded in $CDCl_3$ with added $Eu(fod)_3$) of the Mosher ester from racemic **18a** displayed two singlets separated by 0.6 ppm; the corresponding ester from optically active **18a*** showed *only* the downfield singlet under the same conditions.

(*S*)-(+)-6-((*tert*-Butyldimethylsilyl)oxy)-1-heptyne (18b*). Alcohol **18a*** (6.66 g, 59 mmol) in 28 mL of dimethylformamide containing 4.2 g (62 mmol) of imidazole was treated with 9.3 g (62 mmol) of *tert*-butyldimethylchlorosilane.[23] Completion of the transformation as described above for **18b** afforded 0.38 g of starting alcohol **18a*** and 10.5 g (83% based on consumed **18a***) of **18b***, having IR and ^1H NMR spectra identical with those of the previously obtained racemic material **18b**; $[\alpha]^{20}_D$ +14.5° (*c* 7, dichloromethane).

(*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-(tri-*n*-butyl)stannyl-1-heptene (19*). The above acetylene **18b*** (10.5 g, 46 mmol) was treated with 14.8 g (50 mmol) of tributyltin hydride and 80 mg of azobis(isobutyronitrile) (AIBN).[24] Completion of the transformation as described above for **19** afforded 23.6 g (98%) of **19*** having IR and ^1H NMR spectra identical with those of the previously obtained racemic material **19**.

n*-Butyl ([1*S*,2*R*]-2-[(1*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-heptenyl]-4-oxocyclopentyl)acetate (20*).** The reaction was carried out by using 23.3 g (45 mmol) of stannane **19 and 7.7 g (39 mmol) of enone ester **11***, as described above for **20**, and afforded 8.95 g (54%) of **20***: $[\alpha]^{20}_D$ −61° (*c* 7, dichloromethane).[65]

Anal. Calcd for $C_{24}H_{44}O_4Si$: C, 67.86; H, 10.44. Found: C, 68.13; H, 10.51.

n*-Butyl ([1*S*,2*R*,4*R*]-2-[(1*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-heptenyl]-4-hydroxycyclopentyl)acetate (21a*).** An 8.3-g (19.6 mmol) sample of cyclopentanone **20 was treated with 31 mL (20.7 mmol) of a 0.67 M solution of L-Selectride[30] in tetrahydrofuran at −80 °C as described above for the racemic material **21a**. The resultant 7.8-g (94%) mixture of epimeric alcohols was separated as before by refluxing in 800 mL of toluene in the presence of 40 mg of *p*-toluenesulfonic acid to give 1.8 g (28%) of lactone **7***, $[\alpha]^{20}_D$ −16° (*c* 4, dichloromethane),[65] and 5.2 g (67%) of alcohol **21a***, $[\alpha]^{20}_D$ −9.2° (*c* 4, dichloromethane).[65]

n*-Butyl ([1*S*,2*R*,4*R*]-2-[(1*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)acetate (21b)*.** This reaction was carried out as for **21b** by using 2.6 g (6.1 mmol) of alcohol **21a in 10 mL of acetonitrile in the presence of 2.8 g (12 mmol) of silver oxide and 7 mL (112 mmol) of methyl iodide.[33] Chromatography of the crude product afforded 0.78 g (30%) of starting alcohol **21a*** and 1.8 g (67%, or 96% based on consumed **21a***) of **21b***: $[\alpha]^{20}_D$ −12.7° (*c* 3, dichloromethane).[65]

n*-Butyl 2,2-Bis(methylthio)([1*R*,2*S*,4*S*]-2-[(1*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)acetate (22a*).** A 1.78-g (4 mmol) sample of ester **21b was treated as in the preparation of **22a** to give 2.1 g (98%) of **22a***: $[\alpha]^{20}_D$ −7.7° (*c* 4, dichloromethane).[65]

2,2-Bis(methylthio)([1*R*,2*S*,4*S*]-2-[(1*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)ethanal (22b*). Ester **22a*** (2.1 g, 3.9 mmol) was treated at −110 °C in toluene with 6.7 mL (8 mmol) of a 1.2 M toluene solution of diisobutylaluminum hydride, as in the preparation of **22b**, to afford 1.62 g (89%) of **22b***: $[\alpha]^{20}_D$ +0.9° (*c* 4, dichloromethane).[65]

(2*E*)-Ethyl 4,4-Bis(methylthio)-4-([1*R*,2*S*,4*S*]-2-[(1*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-heptenyl]-4-methoxycyclopentyl)-2-butenoate (22c*). A 1.61-g (3.5 mmol) sample of aldehyde **22b*** in tetrahydrofuran was added to ethyl lithio(trimethylsilyl)acetate [from 840 μL (4.6 mmol) of ethyl (trimethylsilyl)acetate and 4.12 mL (4 mmol) of a 0.97 M tetrahydrofuran solution of lithium diisopropylamide][43] in tetrahydrofuran, as described for **22c**, to produce 1.66 g (89%) of **22c***: $[\alpha]^{20}_D$ −19.7° (*c* 7, dichloromethane).[65]

Anal. Calcd for $C_{27}H_{50}O_4S_2Si$: C, 61.08; H, 9.49; M_r 530.2919. Found: C, 61.49; H, 9.51; M_r (mass spectrum) 530.2943.

(2*E*)-Ethyl 4,4-Bis(methylthio)-4-([1*R*,2*S*,4*S*]-2-[(1*E*,6*S*)-6-hydroxy-1-heptenyl]-4-methoxycyclopentyl)-2-butenoate (23a*). A 1.6-g (3 mmol) sample of silyl ether **22c*** in 30 mL of 3:1 acetic acid–water was treated as described above for **23a** to yield 1.26 g (100%) of **23a***: $[\alpha]^{20}_D$ −23.3° (*c* 5, dichloromethane).[65]

(2*E*)-4,4-Bis(methylthio)-4-([1*R*,2*S*,4*S*]-2-[(1*E*,6*S*)-6-hydroxy-1-heptenyl]-4-methoxycyclopentyl)-2-butenoic Acid (23b*). Ester **23a*** (1.23 g, 3 mmol) in 50 mL of methanol was treated with a solution of 0.6 g (14 mmol) of lithium hydroxide monohydrate in 15 mL of water. After 24 h at 25 °C, the reaction mixture was treated as described above for **23b** to afford 1.12 g (98%) of **23b***: $[\alpha]^{20}_D$ −4° (*c* 9, dichloromethane).[65]

(2*E*,6*S*,10*E*,11a*S*,13*S*,14a*R*)-1,1-Bis(methylthio)-1,6,7,8,9,11a,12,13,14,14a-decahydro-13-methoxy-6-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-4-one (24a*). A 1.08-g (2.8 mmol) sample of acid **23b*** was converted to the corresponding 2-pyridinethiol ester as described above for **24a**. The lactonization was effected in four portions, each of 0.7 mmol of the 2-pyridinethiol ester (each addition over 18 h to 400 mL of refluxing xylene), to yield 46 mg (4.5%) of the enantiomer of 15-epi-**24a***, $[\alpha]^{20}_D$ −43° (*c* 4, dichloromethane), and 522 mg (51%) of **24a***, $[\alpha]^{20}_D$ +128° (*c* 3, dichloromethane). Both products had IR and ^1H NMR spectra identical with those of the previously obtained corresponding racemic compounds.

(2*E*,6*S*,10*E*,11a*S*,13*S*,14a*R*)-13-Methoxy-6-methyl-7,8,9,11a,12,13,14,14a-octahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-(6*H*)-dione (24b*). A solution of 499 mg (1.35 mmol) of lactone **24a***

(65) Although the corresponding product in the racemic series is a 1:1 mixture of diastereomers, the IR and ^1H NMR spectra of this optically active compound (92:8 mixture of diastereomers) were identical with those of the racemic material. The optical rotation is of the 92:8 mixture of diastereomers. No separation of diastereomers was observed on TLC.

in 5 mL of acetonitrile was added to a solution of 720 mg (5.4 mmol) of *N*-chlorosuccinimide and 1.03 g (6.1 mmol) of silver nitrate in 25 mL of 8:2 acetonitrile–water at −5 °C.[47] After being stirring for 0.5 h at −5 °C and 1 h at room temperature, the mixture was treated with 30 mL of ether and then 3 mL of a saturated aqueous solution of sodium sulfite. The crude product was isolated with ether and was purified by silica gel chromatography with 30% ether in pentane to yield 283 mg (72%) of **24b*** having IR and ^{1}H NMR spectra identical with those of the previously obtained racemic **24b**. Lactone **24b***: $[\alpha]^{20}_D$ −45° (*c* 5, dichloromethane).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.25; H, 8.40.

(1*R*,2*E*,6*S*,10*E*,11a*S*,13*S*,14a*R*)-1,6,7,8,9,11a,12,13,14,14a-Decahydro-1-hydroxy-13-methoxy-6-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-4-one (24c*). A 253-mg (0.87 mmol) sample of **24b*** in 9 mL of methanol at −110 °C was treated with 40 mg (1.05 mmol) of sodium borohydride and then stirred for 45 min at −110 °C. Acetone (500 μL) was then added, and the reaction mixture was allowed to warm to room temperature. The crude product was isolated with ethyl acetate and was purified by medium-pressure liquid chromatography with 2% methanol in dichloromethane to give 243 mg (95%) of **24c***: mp 82–82.5 °C (ether–pentane); $[\alpha]^{20}_D$ +92° (*c* 3, dichloromethane). The IR (film) and ^{1}H NMR spectra of **24c*** were identical with those of the previously obtained racemic **24c**.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.27; H, 8.76.

(1*R*,2*E*,6*S*,10*E*,11a*S*,13*S*,14a*R*)-1,6,7,8,9,11a,12,13,14,14a-Decahydro-1,13-dihydroxy-6-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-4-one [(+)-Brefeldin-A] (1*). A 30-mg (0.1 mmol) sample of methyl ether **24c*** in 1 mL of acetonitrile was treated with 250 μL of a 20% solution of (*N*-trimethylsilyl)diethylamine in pentane and then left for 15 h at room temperature.[49] Removal of volatiles under reduced pressure left the crude silyl ether of **24c***. This residue was dissolved in 1.5 mL of dry acetonitrile and was treated, protected from light at room temperature under argon, with 45 mg (0.3 mmol) of dry sodium iodide and 40 μL (0.3 mmol) of freshly distilled chlorotrimethylsilane.[50] After the reaction mixture was stirred for 1 h, an additional 30 mg (0.2 mmol) of sodium iodide and 26 μL (0.2 mmol) of chlorotrimethylsilane were added, and stirring was continued for 2.25 h. Water (1 mL) and ethyl acetate (5 mL) were added to the mixture, which was then extracted with ethyl acetate. The organic phase was washed with sodium thiosulfate and brine and dried over magnesium sulfate. Removal of the solvent and rapid filtration of the residue over a small amount of silica gel with 50% methanol in methylene chloride afforded a mixture of **24c*** and **1***. Separation of the mixture by HPLC (Whatman Partisil M9 10/50 ODS2, 80% methanol–20% water; retention times: **1***, 12 min; **24c***, 18 min at 3 mL/min) afforded 5.2 mg (17%) of starting material **24c*** and 16.1 mg (56%, or 68% based on consumed **24c***)[66] of (+)-brefeldin-A (**1***): mp 204–205 °C (ethyl acetate) (lit.[1c] mp 204–205 °C); mmp 204–205 °C; $[\alpha]^{20}_D$ +93° (*c* 2, methanol) [authentic sample: +93° (*c* 2, methanol)]. The IR (KBr) and ^{1}H NMR (CD_3OD) spectra were identical in all respects with those of an authentic sample. In addition, an admixture of the synthetically and naturally derived compounds was chromatographically (TLC, HPLC) inseparable in a number of different solvent systems.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.56.

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Registry No. 1, 62989-97-3; **1***, 20350-15-6; **7**, 82679-38-7; **7***, 82729-87-1; **10**, 694-98-4; **10***, 16620-79-4; **11**, 76101-85-4; **11***, 82729-81-5; **14a**, 76101-83-2; **14c** (R = C_4H_9), 76101-84-3; **15**, 1193-18-6; **16**, 21889-89-4; **17**, 928-39-2; **18a**, 69177-44-2; **18a***, 65756-08-3; **18b**, 82679-36-5; **18b***, 82729-82-6; (*E*)-**19**, 82679-37-6; (*E*)-**19***, 82729-83-7; **20**, 76110-77-5; **20***, 82729-84-8; **21a**, 76101-86-5; **21a***, isomer 1, 82729-85-9; **21a***, isomer 2, 82729-86-0; **21b**, 76101-87-6; **21b***, 82729-88-2; **22a**, 76101-88-7; **22a***, 82729-89-3; **22b**, 76101-89-8; **22b***, 82729-90-6; **22c**, 76101-90-1; **22c***, 82729-91-7; **23a**, 76101-91-2; **23a***, 82729-92-8; **23b**, 76101-92-3; **23b**, 2-pyridinethiol ester, 82679-39-8; **23b***, 82729-93-9; **23b***, 2-pyridinethiol ester, 82729-94-0; **24a**, isomer 1, 76101-93-4; **24a**, isomer 2, 82729-77-9; **24a***, isomer 1, 82729-95-1; **24a***, isomer 2, 82730-74-3; **24b**, isomer 1, 76101-94-5; **24b**, isomer 2, 82729-78-0; **24b***, 82729-96-2; **24c**, 76101-95-6; **24c***, 82729-97-3; **25***, 1517-7-5; **26***, 15754-50-4; **27***, 82679-40-1; **28***, 82691-61-0; **29a***, isomer 1, 82679-41-2; **29a***, isomer 2, 82679-42-3; **29b***, isomer 1, 82729-79-1; **29b***, isomer 2, 82729-80-4; 2-chloroacrylonitrile, 920-37-6; cyclopentadiene, 542-92-7; 2-chloro-2-cyanobicyclo[2.2.1]hept-5-ene, 6945-87-5; pentynylcopper, 19093-51-7; methyl methanethiosulfonate, 2949-92-0; ethyl (trimethylsilyl)acetate, 4071-88-9; 2-thiopyridyl chloroformate, 73371-99-0; acryloyl chloride, 814-68-6; 1-iodobutane, 542-69-8.

(66) In another run (30.5 mg), the yield of (+)-brefeldin-A (**1***) was 77% (63% conversion).

Nucleotidophospholipids: Oligonucleotide Derivatives with Membrane-Recognition Groups

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Abstract: The synthesis of nucleotidophospholipids, a new type of structure, is reported. In these compounds, the primary or secondary alcohol functions of a dinucleotide, thymidylyl(3′→5′)thymidine, are esterified by the optically active 1,2-diacylglycerophosphoric acid having the chirality of the phospholipids present in biological membranes. The ultraviolet spectrum, circular dichroism, and optical rotatory dispersion of the nucleotidophospholipids in chloroform/methanol solution are described.

The synthesis of unsymmetrical phosphodiesters by means of cyclic enediol phosphoryl (CEP) derivatives involves three basic steps, which can be carried out in one or two laboratory operations depending on the complexity of the two alcohols that are to be joined by the phosphate bond.[1] In general, the first intermediate that is subjected to purification is the acyclic dialkyl 3-oxo-2-butyl phosphate.

Three CEP reagents have been developed to implement this synthetic strategy:[2] the crystalline pyrophosphate (CEP-O-CEP), the liquid phosphorochloridate (CEP-Cl), and the crystalline phosphoroimidazole (CEP-$N_2C_3H_3$). The pyrophosphate and phosphorochloridate are used in conjunction with triethylamine, which functions as Proton Sponge in the first step and as catalyst

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