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Published on Web 11/27/2002

First Comprehensive Bakkane Approach: Stereoselective and Efficient Dichloroketene-Based Total Syntheses of (±)- and (−)-9-Acetoxyfukinanolide, (±)- and (+)-Bakkenolide A, (−)-Bakkenolides III, B, C, H, L, V, and X, (±)- and (−)-Homogynolide A, (±)-Homogynolide B, and (±)-Palmosalide C

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Received June 17, 2002

Abstract: Cycloaddition of dichloroketene with dimethylcyclohexenes has been used as the key reaction in an efficient, general approach to the bakkanes. New methods and methodologies that have been developed in this work include spiro β-methylene-γ-butyrolactonizations, a vicinal dicarboxylation, an angelic ester preparation, a transesterification, an epoxy ketone double reduction, and a retro aldol−aldol approach to low-energy aldol isomers.

Introduction

The bakkane family comprises sesquiterpenes that have in common a hydrindane skeleton and a spiro-fused γ-butyrolactone that generally bears an otherwise rare β-methylene function.[1] The archetype of this family, bakkenolide A (fukinanolide) (**1***, Chart 1),[2] was first isolated in 1968 from the flower stalks of the wild butterbur *Petasites japonicus* by two Japanese groups working independently.[3]

Over the next three decades, several more complex bakkanes were isolated, including (−)-homogynolide A (**2a***),[4] (−)-homogynolide B (**2b***),[4] (+)-palmosalide C (**3**),[5] (−)-9-acetoxyfukinanolide (**4***),[6] and (−)-bakkenolides III and B−E (**5a**−**e***).[3b−d,4,7] The number of known bakkanes, however, truly mushroomed in 1999 with Wu and co-workers' publications on the root constituents of *Petasites formosanus* Kitamura.[8] Thirty-five new bakkanes were disclosed, primarily additional C-1 and/or C-9 oxygenated congeners of bakkenolide A (e.g., **5f**−**i***), thus bringing the total number of known bakkanes to approximately 50. While most of these have to date been isolated from plants indigenous to Japan and Taiwan, plants native to China, The Czech Republic, France, Iran, Norway, Scotland, Spain, and Switzerland and an octocoral found in the Indian Ocean have also yielded various bakkanes.[1b]

Through a combination of degradation, spectroscopic, and X-ray diffraction studies, the structure and the relative and absolute stereochemistry of bakkenolide A were determined;[3] it would now appear that most, if not all, of the bakkanes belong to this enantiomeric series. Furthermore, among the known bakkanes, only two are not β-methylene-γ-butyrolactones, and these are also the only ones to have inverted stereochemistry at

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(1) See: (a) Fischer, N. H.; Oliver, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2. (b) Silva, L. F., Jr. *Synthesis* **2001**, 671−689.

(2) An asterisk with a compound number signifies that a single enantiomer is depicted with the absolute stereochemistry as indicated. Bakkane numbering is used in this paper.

(3) (a) Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, *9*, 369−373. (b) Shirahata, K.; Kato, T.; Kitahara, Y.; Abe, N. *Tetrahedron* **1969**, *25*, 3179−3191 and 4671−4680. (c) Naya, K.; Takagi, I.; Hayashi, M.; Nakamura, S.; Kobayashi, M.; Katsumura, S. *Chem. Ind. (London)* **1968**, 318−320. (d) Naya, K.; Hayashi, M.; Takagi, I.; Nakamura, S.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3673−3685. This plant is known vernacularly in the north-east of Japan as "bakka", but as "fuki" in Japanese, and thus an often confusing dual nomenclature has arisen for several members of this family.

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(5) Wiemer, D. F.; Wolfe, L. K.; Fenical, W.; Strobel, S. A.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 1973−1976.

(6) Naya, K., Kawai, M.; Naito, M.; Kasai, T. *Chem. Lett.* **1972**, 241−244.

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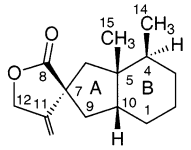
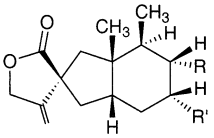
(8) (a) Wu, T.-S.; Kao, M.-S.; Wu, P.-L.; Lin, F.-W.; Shi, L.-S.; Teng, C.-M. *Phytochemistry* **1999**, *52*, 901−905. (b) Wu, T.-S.; Kao, M.-S.; Wu, P.-L.; Lin, F.-W.; Shi, L.-S.; Liou, M.-J.; Li, C.-Y. *Chem. Pharm. Bull.* **1999**, *47*, 375−382.

Chart 1

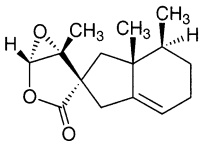


1* (+)-Bakkenolide A

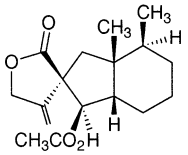


2a*, R = H; R' = OCOC(CH$_3$)=CHCH$_3$ (*Z*)
(–)-Homogynolide A

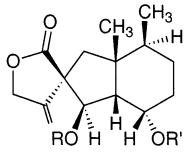
2b*, R = OCOC(CH$_3$)=CHCH$_3$ (*E*); R' = H
(–)-Homogynolide B



3 (+)-Palmosalide C



4* (–)-9-Acetoxyfukinanolide

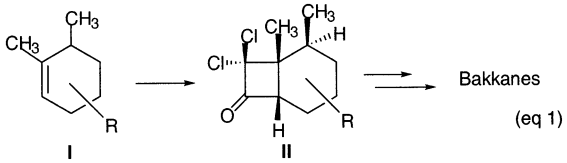


5a*, R = R' = H (–)-Bakkenolide III
b*, R = COCH$_3$; R' = COC(CH$_3$)=CHCH$_3$ (*Z*) (–)-Bakkenolide B
c*, R = H; R' = COC(CH$_3$)=CHCH$_3$ (*Z*) (–)-Bakkenolide C
d*, R = COCH$_3$; R' =COCH=CHSCH$_3$ (*Z*) (–)-Bakkenolide D
e*, R = COCH$_3$; R' = COC(CH$_3$)=CHCH$_3$ (*E*) (–)-Bakkenolide E
f*, R = R' = COCH(CH$_3$)$_2$ (–)-Bakkenolide H
g*, R = R' = COCH$_3$ (–)-Bakkenolide L
h*, R = H; R' = COCH$_2$CH(CH$_3$)$_2$ (–)-Bakkenolide V
i*, R = H; R' = COCH$_3$ (–)-Bakkenolide X

the C-7 spiro center.[5,9] While the biogenesis of the bakkanes hasnot been firmly established, they are believed to issue from the eremophilanes, compounds with which they frequently coexist.[3,5−7,9,10] Diverse biological properties have been attributed to members of the bakkane family, including selective cytotoxic activity,[8b,11] antifeedant effects,[12] and inhibition of platelet aggregation,[8a] traits generally associated with the conjugated α-methylene-γ-butyrolactones.

Evans and Sims in 1973 published the first successful bakkane total synthesis, a 13-step preparation of racemic bakkenolide A that proceeded in ca. 1.5% overall yield, with a novel [2,3]-sigmatropic rearrangement as the key transformation.[13] Remarkably, our disclosures[14a,b] on the synthesis of racemic bakkenolide A in 1985 and the first synthesis of (+)-bakkenolide A in 1988 were the next publications in this area. Since this period, however, synthetic activity has increased considerably, with publications from several laboratories[15] in addition to our own.[14c−i]

Our general interest in the bakkanes, initially in bakkenolide A, originated from a desire to exploit further the synthetic potential of dichloroketene and its cycloadducts.[16,17] Because of the propensity of this ketene to undergo for stereoelectronic reasons axial carbonyl bonding and to prefer due to electronic factors adjacency of the Cl_2C group to the olefinic carbon that is better able to stabilize an incipient positive charge,[17,18] it appeared that its cycloaddition with 1,6-dimethylcyclohexene, as well as certain derivatives, might proceed highly stereo- (and regio-) selectively to give adduct **II**, in which three or more of the stereocenters of the bakkanes would be in place with the correct relative configurations (eq 1).



1-Methylcyclohexene was known[19] to undergo smooth cycloaddition with dichloroketene to give the expected dichlorocyclobutanone adduct; it was anticipated that the additional C-6

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(15) (a) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S. *Tetrahedron Lett.* **1994**, *35*, 429−432 ((±)-homogynolide B). (b) Srikrishna, A.; Reddy, T. J.; Nagaraju, S.; Sattigeri, J. A. *Tetrahedron Lett.* **1994**, *35*, 7841−7844 ((±)-bakkenolide A). (c) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 469−470 ((±)-4-*epi*-bakkenolide A). (d) Srikrishna, A.; Reddy, T. J. *Indian J. Chem.* **1995**, *34B*, 844−846 ((−)-homogynolide A). (e) Mori, K.; Matsushima, Y. *Synthesis* **1995**, 845−850 ((−)-homogynolide A). (f) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069−2076 ((±)-homogynolide B). (g) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806−3814. Back, T. G.; Payne, J. E. *Org. Lett.* **1999**, *1*, 663−665. Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361−4368 ((±)-bakkenolide A).
(16) For leading references to our work with dichloroketene, see: Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443.
(17) For reviews on dichloroketene, see: Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159−646. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.
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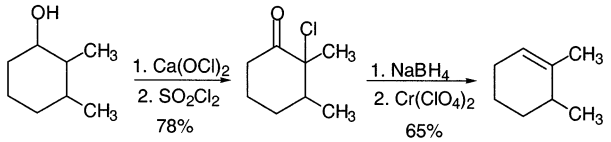
methyl group would prove innocuous and, furthermore, that the cycloaddition would take place principally trans to this group for stereoelectronic reasons. If this were, in fact, observed, it was hoped that methods could then be developed for regioselectively converting the dichlorocyclobutanones **II** into five-membered carbocycles that would possess appropriate functionalization to allow facile construction of the spiro-fused γ-butyrolactone unit and, ultimately, the natural products.

In this paper, we provide full details of a comprehensive bakkane approach that we have been able to develop over the past several years through the successful implementation of this general strategy. Described below, in addition to the preparation of (±)- and (+)-bakkenolide A, are *the first syntheses of representatives of the more highly oxygenated bakkanes*: (±)- and (−)-homogynolide A, (±)-homogynolide B, (±)-palmosalide C, (±)- and (−)-9-acetoxyfukinanolide, and (−)-bakkenolides III, B, C, H, L, V, and X (Chart 1).[14] As will be noted, the stereoselective nature of these syntheses results from our being able to parlay through internal asymmetric induction the stereoselectivity of the above-mentioned dichloroketene-olefin [2 + 2] cycloaddition; the efficiency stems from several new synthetic methods that were developed in the context of this work.

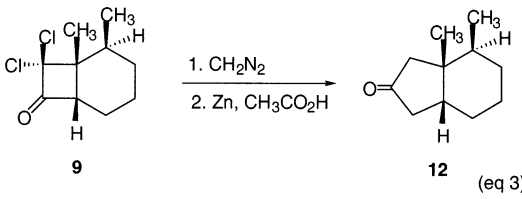
Results and Discussion

Bakkenolide A. The required 1,6-dimethyl-1-cyclohexene (**8**) was best prepared by the route shown in eq 2. Cheap 2,3-

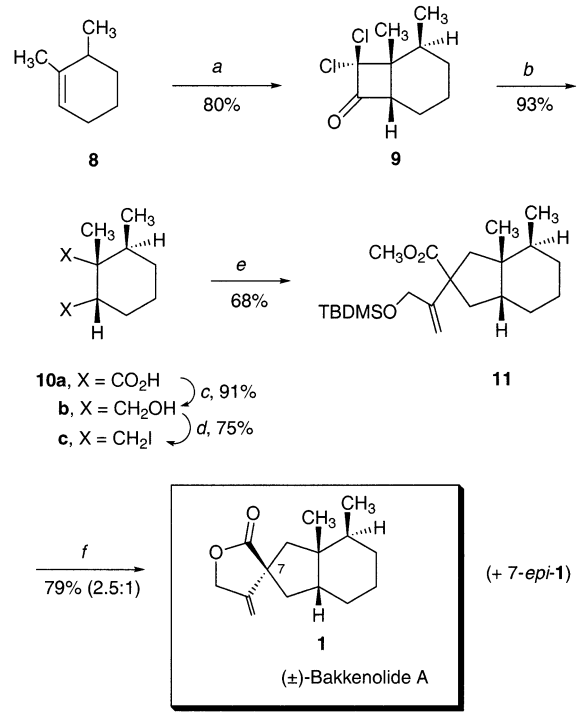


dimethylcyclohexanol (**6**) was oxidized[20] on a large scale to provide a diastereomeric mixture of ketones, which underwent highly regioselective chlorination with sulfuryl chloride[21] to give **7**. Reduction[22] of this material in two stages then provided the desired olefin **8** in ca. 50% overall yield with an isomeric purity in excess of 96% following distillation. Other preparations were considerably less regioselective and, in addition, less conducive to large-scale work and facile olefin isolation.

To our considerable satisfaction, this olefin indeed underwent highly regio- and stereoselective cycloaddition (≥90%) in the presence of trichloroacetyl chloride, phosphorus oxychloride, and zinc−copper couple[19a] to deliver the desired adduct **9** in 80% yield (Scheme 1). A minor amount of an inseparable isomer (later determined to be the diastereomer) could be detected by ^{1}H NMR, but over the course of the remainder of the synthesis, conveniently, this material gradually filtered out. That the major product was, in fact, the desired diastereomer was readily demonstrated by conversion[19b] to the known[23] bicyclo[4.3.0]-nonanone **12** (eq 3).

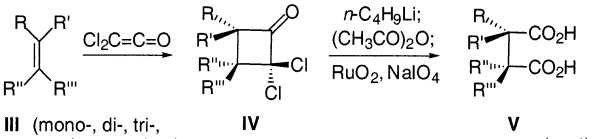


Scheme 1 [a]



[a] (a) CCl_3COCl, Zn−Cu, $POCl_3$, $(C_2H_5)_2O$, 20 °C. (b) *n*-BuLi, THF, −78 °C, then $(CH_3CO)_2O$, −78 → 20 °C; RuO_2 (cat), $NaIO_4$, CH_3CN−CCl_4−H_2O (1.5:1:1), 20 °C. (c) $LiAlH_4$, THF, Δ. (d) TMSI, $CHCl_3$, 20 °C. (e) **13**, DME−HMPA, LHMDS (2×), −60 °C. (f) HF, CH_3CN, 20 °C, separation.

We envisioned at this point transformation of dichlorocyclobutanone **9** into a bis-electrophile for five-membered ring formation and rapid access to the bakkane framework by reaction with a β-methylene-γ-butyrolactone synthon. Working with model systems, a simple and reliable one-pot protocol was developed for the oxidative cleavage of a wide range of α,α-dichlorocyclobutanones: sequential treatment with *n*-butyllithium, acetic anhydride, and ruthenium dioxide-sodium periodate cleanly provided the corresponding succinic acids **V** in 73−94% yields (eq 4).[24] It is worth pointing out that this dichloroketene cycloaddition-cleavage tandem (**III** → **V**) is tantamount to a stereospecific vicinal dicarboxylation procedure, for which little else exists.



Application of the cleavage method to the above adduct **9** delivered the expected diacid **10a**, which could be readily reduced to the corresponding diol **10b** in excellent overall yield. The bis-electrophile cyclization substrate, diiodide **10c**, was next prepared in 75% yield with trimethylsilyl iodide in chloroform.[25]

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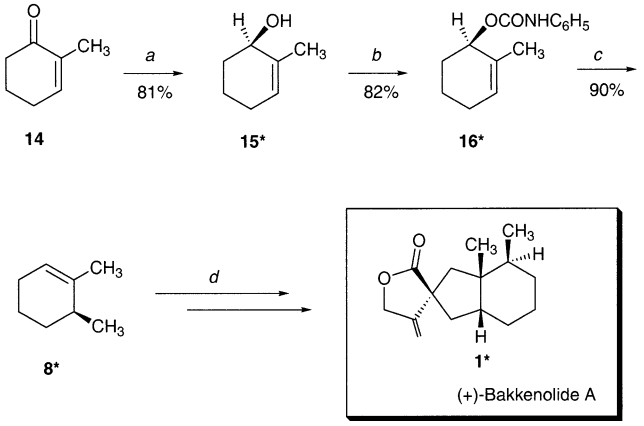
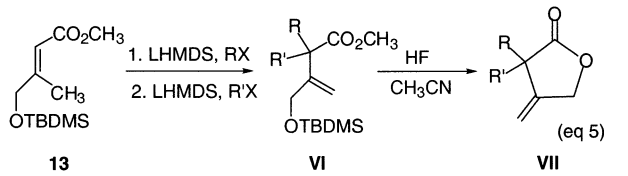
Scheme 2 [a]



[a] (a) $LiAlH_4$, 2-(ethylamino)pyridine, (−)-*N*-methylephedrine, $(C_2H_5)_2O$, −78 °C. (b) C_6H_5NCO, $(C_2H_5)_2O$, 20 °C; recryst. (c) $Li(CH_3)_2Cu$, $(C_2H_5)_2O$, 0 → 20 °C. (d) As in Scheme 1.

Several other procedures were also tested for this conversion, but they produced substantial amounts of the corresponding tetrahydrofuran.

The next challenge, finding a linchpin for forming the five-membered carbocycle that would, in addition, provide for facile construction of the β-methylene-γ-butyrolactone, was also subjected to a separate study. Although neither β-methylene-γ-butyrolactone itself nor β-methyl-α,β-butenolide proved useful, due to instability toward conjugation and preferential endocyclic proton loss, respectively, the easily prepared acrylate derivative **13** was found to be a general β-methylene-γ-butyrolactonization reagent (eq 5). A variety of these lactones could be prepared in 44−81% overall yields.[26]



Pleasingly, when diiodide **10c** was subjected to this new lactonization approach, a 2:1 mixture of racemic bakkenolide A (**1**) and its C-7 epimer was obtained in 54% yield. This selectivity, while modest, can be explained by evoking a U-shaped ester dienolate[27] and a preferred reactive conformation for ring closure that avoids bringing the silyloxymethyl and angular methyl groups into proximity. By using DME-HMPA at −58 °C in place of THF−HMPA at −78 °C, the epimeric ratio could be slightly improved to 2.5:1 without modification of the overall yield. Changes in the counterion and/or the protecting group, like solvent modification, had surprisingly little effect on the reaction outcome. Racemic bakkenolide A, readily obtained from the mixture by crystallization from cold pentane, was found to be in all respects (other than mp and optical rotation) identical to an authentic sample of natural bakkenolide A.

This short, efficient preparation of the racemic product (six steps, 10% yield) could be easily translated into the first total synthesis of (+)-bakkenolide A (Scheme 2). 2-Methyl-2-cyclohexen-1-one[28] was asymmetrically reduced with lithium aluminum hydride that had been pretreated with (−)-*N*-methylephedrine and 2-(ethylamino)pyridine, as described by Terashima and co-workers,[29] to give in 81% yield and ≥95% ee (*R*)-2-methyl-2-cyclohexen-1-ol (**15***), which was then converted into *N*-phenylcarbamate **16*** (82% yield). This derivative was treated with lithium dimethylcuprate in ether to afford, through a highly syn S_N2'-selective intramolecular methyl delivery,[30] (*S*)-1,6-dimethyl-1-cyclohexene (**8***) in 90% yield.[31] Conversion of this olefin into (+)-bakkenolide A (**1***) was effected as in the racemic series to give material (mp 80−80.5 °C, $[\alpha]_D$ +18) chromatographically and spectroscopically indistinguishable from the naturally derived product (mp 80.5−80.6 °C, $[\alpha]_D$ +17[3d]).

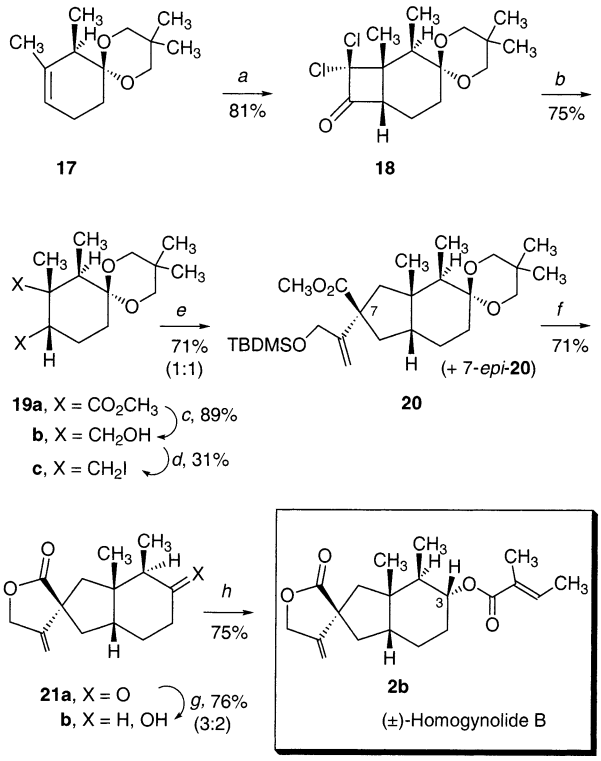
Homogynolide B. Encouraged by the bakkenolide A success, we next targeted certain of the more highly oxygenated bakkanes, starting with homogynolide B (**2b***, Chart 1), a C-3 oxygenated derivative that had been isolated from *Homogyne alpina*[4] and found to possess significant antifeedant activity against a number of grain and feed pests.[12] It was initially hoped that the synthesis of homogynolide B might be readily accomplished from a *trans*-2,3-dimethyl-3-cyclohexen-1-ol derivative by simply repeating the steps used in the bakkenolide A approach. This proved optimistic, however. 2,3-Dimethyl-3-cyclohexen-1-one could be easily prepared from 2,3-dimethylanisole under Birch conditions,[32] but clean, selective reduction to the corresponding trans alcohol could not be realized; in addition, several inversion attempts on derivatives of the cis alcohol (secured selectively with L-Selectride) resulted mainly in elimination.

It was reasoned that with an acetal protecting group, the introduction of the C-3 asymmetric center could be postponed to a later and perhaps more opportune stage in the synthesis and, additionally, that concomitant hydrolysis of this group and lactonization would probably be feasible. Thus, the dimethyltrimethylene acetal of 2,3-dimethyl-3-cyclohexen-1-one[32] (**17**) was exposed to in situ generated dichloroketene, which smoothly delivered the expected cyclobutanone **18** as the sole product in 81% yield (Scheme 3). The oxidative cleavage of the four-membered ring of this adduct under standard conditions was attended by loss of the acetal protecting group. This problem could be readily overcome, however, by effecting the cleavage with ozone in lieu of ruthenium dioxide-sodium periodate, which gave, following esterification, diester **19a** in 75% yield. Reduction of this material with lithium aluminum hydride then provided in 89% yield the desired diol **19b**.

A consideration at this point was that in a number of previously studied systems, neither the dimesylates nor the iodo mesylates had performed well in cycloalkylations (poor yields, unfavorable diastereoselectivity),[33] which made the diiodide

(26) Greene, A. E.; Coelho, F.; Deprés, J.-P.; Brocksom, T. J. *J. Org. Chem.* **1985**, *50*, 1973−1975.
(27) See: Cainelli, G.; Cardillo, G.; Contento, M.; Trapani, G.; Ronchi, A. U. *J. Chem. Soc., Perkin Trans. 1* **1973**, 400−404 and references therein.
(28) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth.* **1963**, *Coll. Vol. 4*, 162−166.
(29) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239−242. The procedure of Corey and Bakshi was subsequently found to be superior: Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614.
(30) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035−1036. See also: Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715−721.
(31) That little or no erosion of enantiopurity had taken place during this transformation was later established by conversion of the cycloadduct into 1,2-dimethylcyclo[4.3.0]nonan-8-one (**9*** → **12***, eq 3), which was then transformed into its [*R*,*R*]-1,2-dimethylethylene acetal. ^{13}C NMR indicated ≥95/5 diastereomeric purity. See: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183−2186.
(32) Marshall, J. A.; Babler, J. H. *Tetrahedron Lett.* **1970**, *11*, 3861−3864.

Scheme 3 [a]



[a] (a) CCl_3COCl, Zn−Cu, $POCl_3$, $(C_2H_5)_2O$, 20 °C. (b) *n*-BuLi, THF, −78 °C, then $(CH_3CO)_2O$, −78 → 20 °C; O_3, CH_2Cl_2−CH_3OH−C_5H_5N, −78 °C, then CH_3SCH_3, −78 → 20 °C; aqueous NaOH, CH_3I, HMPA, 20 °C. (c) $LiAlH_4$, THF, 20 °C. (d) 1,2-Phenylene phosphorochloridite, C_5H_5N, $(C_2H_5)_2O$, 0 °C; I_2, CH_2Cl_2, 20 °C; $(CH_3)_2C(CH_2OH)_2$, $BF_3{\cdot}O(C_2H_5)_2$, CH_2Cl_2, 0 °C. (e) **13**, THF−HMPA, LHMDS (2×), −78 → 20 °C; separation. (f) HF, CH_3CN, 20 °C. (g) $NaBH_4$, $(CH_3)_2CHOH$, 0 °C; separation (β recycled with PCC, 80%). (h) Tiglic acid, DCC, DMAP, $C_6H_5CH_3$, 65 °C.

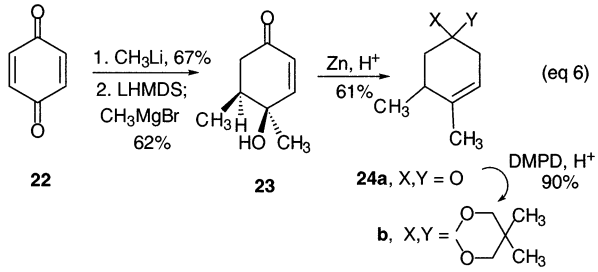
analogous to **10c** desirable.[34] Considerable effort was expended in this direction, but most attempts to prepare diiodide **19c** were thwarted by elimination to give the methylene derivative or cyclization to afford the tetrahydrofuran, both stemming from the slowness of the neopentyl displacement. Fortunately, Corey's phosphite method[35] allowed conversion into the diiodide, albeit in only moderate yield and with attendant loss of the protecting group. Reprotection, however, provided the desired acetal in good yield.

β-Methylene-γ-lactonization of this diiodide began by transformation with acrylate **13** to an equimolar mixture of readily separated epimeric hydrindanes (71% yield). Each was treated with aqueous hydrofluoric acid in acetonitrile, which smoothly effected both double deprotection and lactonization to afford the corresponding keto lactones. The keto lactone (**21a**) from the less polar ester acetal provided spectroscopic data that were perfectly concordant with the literature values for the natural product-derived substance,[4a] whereas the C-7 epimeric lactone from the more polar ester acetal produced data that were clearly different. Reduction of the desired keto lactone with sodium borohydride in 2-propanol then gave in 76% yield a separable 3:2 mixture of β (δ 3.84) and α (δ 3.40 br) hydroxy lactones.[36] The more polar α hydroxy derivative **21b**[4a] was esterified with tiglic acid in the presence of DCC and DMAP in warm toluene[37] to afford in 75% yield racemic homogynolide B, spectroscopically and chromatographically identical to an authentic sample of the natural product.

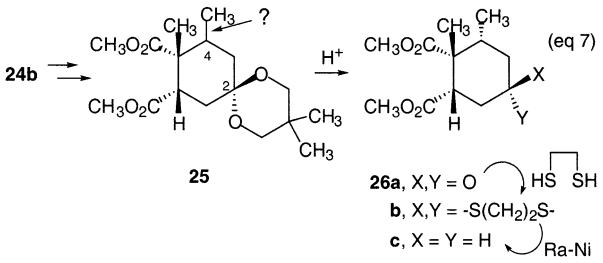
This first synthesis of a functionalized bakkenolide is reasonably short and efficient, proceeding from olefin **17** in 11 steps and ca. 2% overall yield.

Homogynolide A. Homogynolide A (**2a**, Chart 1), a second B-ring oxygenated bakkenolide isolated from *Homogyne alpina*[4] with antifeedant activity against grain and feed pests,[12] appeared to lend itself to straightforward preparation along the lines described for the synthesis of homogynolide B. The structural similarity of these two molecules belied, however, the challenges that lay ahead.

4,5-Dimethyl-3-cyclohexen-1-one (**24a**), which, surprisingly, had not been previously prepared, was accessed from benzoquinone by using the excellent conjugate addition procedure described by Liotta and co-workers,[38] followed by reaction with zinc powder in acetic acid (eq 6). Acetalization of **24a** was then performed with 2,2-dimethylpropane-1,3-diol (DMPD) and *p*-toluenesulfonic acid in refluxing toluene to provide the cyclization substrate, olefin acetal **24b**, in high yield.[39]



To our temporary delight, application of the chemistry employed in the homogynolide B synthesis produced highly stereoselectively and in good overall yield the diester acetal **25** (eq 7). The β configuration at C-4 (bakkane numbering) was

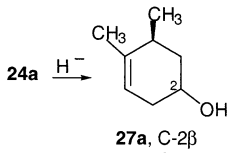


not considered secure, however, because for this outcome dichloroketene has to overcome the presence of an encumbering axial substituent at C-2. Thus, the diester acetal was subjected

(33) (a) Coelho, F. A. Ph.D. Thesis, University of Grenoble, 1987. (b) Hartmann, B. Ph.D. Thesis, University of Grenoble, 1992.
(34) The acetal protecting group turned out to be a particularly fortunate choice in that subsequent work showed the diiodide-acetal pairing to be optimal, others providing without exception unfavorable diastereoselectivities (1:3−5).[33] These diastereomeric ratios, while reflecting rather small differences in transition state energies, indicate nonetheless that subtle conformational and perhaps steric effects operate in reactions of these nonrigid molecules.
(35) Corey, E. J.; Anderson, J. E. *J. Org. Chem.* **1967**, *32*, 4160−4161.
(36) The former could be recycled through PCC oxidation to keto lactone **21a** (80% yield).
(37) See: Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917−5919.
(38) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702−3704.
(39) This acetal could also be prepared from ethyl 5,6-dimethyl-2-oxo-3-cyclohexenecarboxylate (Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. *J. Org. Chem.* **1983**, *48*, 788−790) by decarbethoxylation (DMSO−H_2O, Δ, 90%) followed by acetalization (90%).

to hydrolysis, thioacetalization, and Raney nickel desulfurization to give diester **26c**, which was, in fact, distinctly different from the dimethyl ester of **10a** (Scheme 1).[40] Cycloaddition therefore takes place cis to the C-4 methyl and, to respect both electronic and stereoelectronic requirements,[17,18] must involve a semi-boat conformation. An analogous α-face cycloaddition, also thought to involve a semi-boat conformation, has previously been observed with dichloroketene and 3-methylcholest-2-ene.[18b]

Faced with this impasse, we elected to replace the acetal with a protected β-hydroxyl group to eliminate the presence of an encumbering C-2 axial substituent and thus allow, in all probability, the cycloaddition to proceed with the desired orientation. The reduction of ketone **24a** was studied in some detail, and the results obtained are shown in eq 8. Lithium



Reagent (Conditions)	27a / 27b
$LiAlH_4$ (THF, −78 °C)	49 / 1
$LiAl(O^tC_4H_9)_3H$ (THF, −78 °C)	19 / 1
$NaBH_4$ (CH_3OH, 0 °C)	9 / 1
$LiB(C_2H_5)_3H$ (THF, 0 °C)	4 / 1
LS-Selectride (THF, −78 °C)	1 / 2
LS-Selectride (THF, −100 °C)	1 / 3

(eq 8)

aluminum hydride in THF at −78 °C provided the most favorable β/α ratio of alcohols, as can be seen, and in excellent yield (98%).[41] Conversion of the β alcohol **27a** so obtained into the corresponding benzyl ether **27c** was next readily accomplished in nearly quantitative yield (Scheme 4).

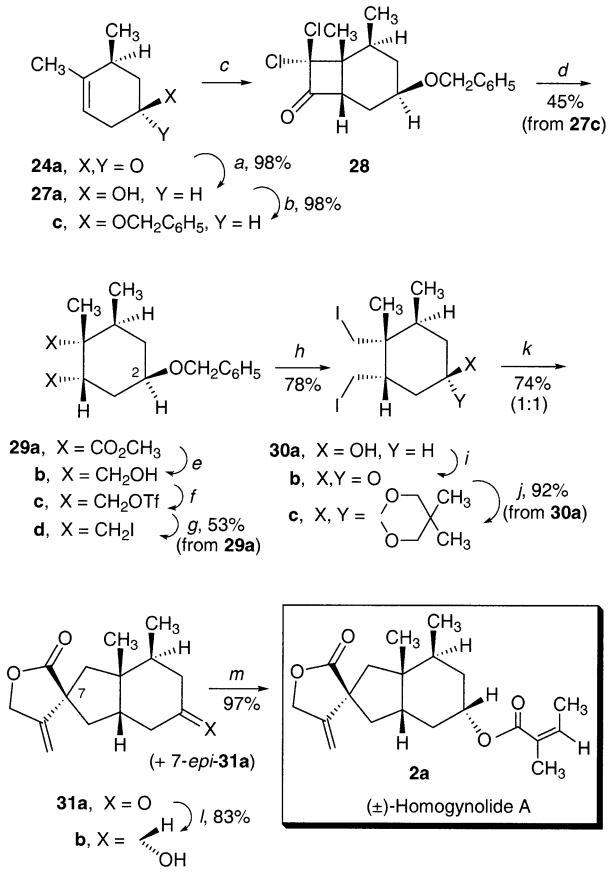
Reaction of this new cycloaddition substrate with in situ generated dichloroketene cleanly afforded a single product, dichlorocyclobutanone **28**, which after oxidative cleavage as with homogynolide B (lithium dimethylcuprate[24] was found to be more effective than *n*-butyllithium) yielded diester **29a**. That this diester could be converted into the dimethyl ester of **10a** (Scheme 1) (H_2, Pd/C; PCC; $HS(CH_2)_2SH$, BF_3; Ra−Ni) served to confirm the expected stereochemical outcome of the cycloaddition. The four chiral centers in diester **29a** are thus introduced with virtually complete stereochemical control; however, that at C-2 must ultimately be adjusted.

The next problem was to prepare a suitable diiodide for reaction with acrylate **13**. Although the previously successful phosphite method[35] and several other iodination procedures failed entirely with diol **29b** (obtained from diester **29a** with lithium aluminum hydride), fortunately the ditriflate of this diol could be prepared and underwent clean double displacement (as opposed to the dimesylate) in the presence of tetrabutylammonium iodide to yield diiodide **29d** in 53% overall yield from the diester.

Aware from our previous work that an acetal at C-2 would probably furnish the best ratio of C-7 epimers, we nonetheless first examined cycloalkylation with this benzyl ether and with the corresponding dimethylthexylsilyl derivative (prepared analogously). Concordant with the earlier findings, however, the ratio of C-7 epimers turned out to be distinctly unfavorable (ca. 1:3), regardless of the experimental conditions employed. Therefore, the C-2 β benzyloxyl substituent, having served its role in the cycloaddition, was now replaced by an acetal group for the purpose of achieving a stereochemically satisfactory cycloalkylation. This switch, which also anticipated the introduction of the required C-2 α oxygen substituent, could be accomplished through sequential debenzylation, oxidation, and acetalization, which gave **30c** in 72% overall yield.[42]

Cyclization of diiodide **30c** under the usual conditions, followed by brief treatment of the resulting esters with aqueous hydrofluoric acid in acetonitrile to effect concomitant double deprotection and lactonization, provided keto lactone **31a**, together with its C-7 epimer, in indeed a much improved ratio and in good overall yield.[43] After separation, keto lactone **31a** was effectively reduced with lithium tri-*tert*-butoxyaluminum hydride with >95/5 stereoselectivity to give in high yield the desired α hydroxy lactone **31b**. In contrast, sodium borohydride in isopropyl alcohol, with or without added cerium trichloride, gave nearly equimolar amounts of the epimeric alcohols.[41] Both keto lactone **31a** and hydroxy lactone **31b** provided spectral

Scheme 4 [a]



[a] (a) $LiAlH_4$, THF, −78 °C. (b) NaH, $C_6H_5CH_2Br$, $(n\text{-}C_4H_9)_4N^+I^-$, THF, Δ. (c) CCl_3COCl, $POCl_3$, Zn−Cu, $(C_2H_5)_2O$, 20 °C. (d) $Li(CH_3)_2Cu$, $(C_2H_5)_2O$, −50 °C, then $(CH_3CO)_2O$, −50 → 20 °C; O_3, CH_2Cl_2−CH_3OH, −78 °C, then CH_3SCH_3, −78 → 20 °C; aqueous NaOH, CH_3I, HMPA, 20 °C. (e) $LiAlH_4$, THF, 20 °C. (f) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, −30 °C. (g) $(n\text{-}C_4H_9)_4N^+I^-$, $C_6H_5CH_3$, 20 °C. (h) $(CH_3)_3SiI$, CH_2Cl_2, 20 °C. (i) PCC, CH_2Cl_2, 20 °C. (j) $(CH_3)_2C(CH_2OH)_2$, $BF_3{\cdot}O(C_2H_5)_2$, CH_2Cl_2, 0 °C. (k) **13**, LHMDS (2 equiv), DME−THF−HMPA, −58 °C; aqueous HF, CH_3CN, 20 °C, separation. (l) $LiAl(O\text{-}t\text{-}C_4H_9)_3H$, THF, 0 °C. (m) **32**, $C_6H_5CH_3$, 70 °C.

(40) That this was indeed the epimer at C-4 and not at C-10 was proven by comparison with an authentic sample of trans diester, obtained by base treatment of the dimethyl ester of **10a**.

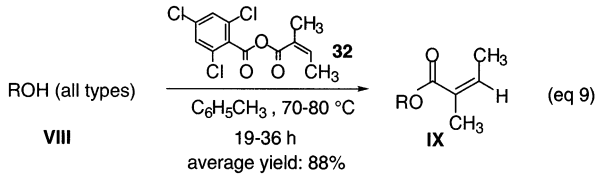
(41) For a discussion of diastereoselectivity in the reduction of cyclic ketones with metal hydrides, see: Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1995; pp 100−121.

(42) Attempted preparation of diiodide **30c** from the C-2 acetal corresponding to **29b** failed due to competing reactions during ditriflate formation.

(43) While the overall yield remained relatively constant (ca. 75%), the ratio varied experimentally from 3:1 to 1:1.

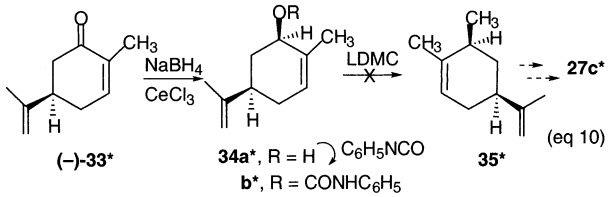
data in excellent agreement with the literature values[4a] for the products derived from natural homogynolide A.

The remaining transformation, conversion of hydroxy lactone **31b** into homogynolide A, required the development of a new procedure for the preparation of angelate esters. Existing procedures[44] were unsatisfactory, often producing large amounts of the thermodynamically more stable tiglate ester; attempted formation of homogynolide A from hydroxy lactone **31b** by using angelic acid in the presence of DCC and DMAP, for example, yielded only the tiglate ester. After some study, it was discovered that by employing the mixed Yamaguchi anhydride[45] derived from angelic acid and 2,4,6-trichlorobenzoyl chloride in dry toluene at 70−80 °C *in the absence of free base*, a range of alcohols could be converted into their angelate esters in excellent yields and without even a trace amount of tiglate ester contamination (eq 9).[46] Application of this procedure to the



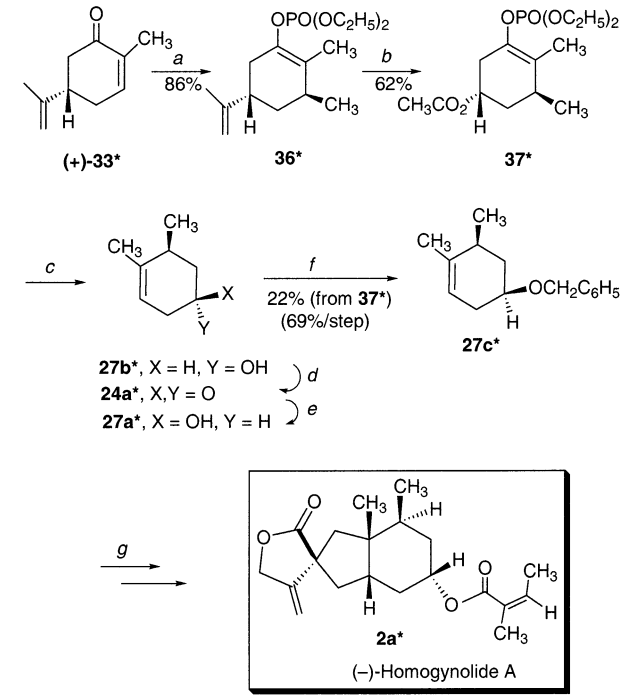
problem at hand was quite successful and provided in 97% yield racemic homogynolide A, whose identity was established through direct spectral comparison with the natural substance.

The respectable efficiency of this first synthesis of the homogynolide A (15 steps, 2% overall yield) prompted us to use it for the preparation of the natural substance. With the idea of exploiting the chiral pool for securing olefin **27c***, (−)-carvone[47] was considered a possible starting material: stereoselective reduction to give (−)-*cis*-carveol, followed by application of the previously used method of Gallina and Ciattini[30] (see **16*** → **8***, Scheme 2) and degradation of the isopropenyl group of the resulting diene, it seemed, could yield the desired olefin. Luche reduction[48] of (−)-carvone ((−)-**33***, eq 10) did cleanly afforded the cis alcohol; however, the *N*-phenylcarbamate derivative **34b*** proved to be totally unreactive in the presence of lithium dimethylcuprate (LDMC), probably due to the high energy transition-state conformation (1,3-diaxial interaction) required to form the product **35***. This result, together



with the difficulty encountered in efficiently degrading the isopropenyl group in the presence of the trisubstituted endocyclic double bond (using limonene as a model), led us to study an alternative, conjugate-addition approach from (+)-carvone ((+)-**33***) (Scheme 5).

Scheme 5 [a]



[a] (a) $Li(CH_3)_2Cu$, $(C_2H_5)_2O$, 0 → 20 °C, then $ClPO(OC_2H_5)_2$, HMPA, −50 → 20 °C. (b) O_3, $CH_2Cl_2-CH_3OH-C_5H_5N$, 20 °C, then *p*-$NO_2C_6H_4$-COCl, $CH_2Cl_2-C_5H_5N$, −30 °C → reflux. (c) Li, CH_3NH_2, THF−*t*-$C_4H_9OH-(C_2H_5)_2O$, −78 → −15 °C. (d) H_2CrO_4, $(C_2H_5)_2O$, 0 °C. (e) $LiAlH_4$, THF, −78 °C. (f) NaH, $C_6H_5CH_2Br$, $(n\text{-}C_4H_9)_4N^+I^-$, THF, Δ. (g) As in Scheme 4.[51]

Conjugate addition of lithium dimethylcuprate to (+)-carvone,[47,49] followed by enolate trapping with diethyl chlorophosphate, gave stereoselectively and in high yield enol phosphate **36***. Ozonolysis of this diene proceeded selectively in the desired sense, due to a now deactivated endocyclic double bond, to give in 85% yield the acetyl-substituted derivative. Even better, however, was that when the intermediate hydroperoxide was subjected to Criegee rearrangement,[50] the acetoxy-substituted derivative **37*** was produced directly in 62% yield. Birch reduction of this material in methylamine conveniently provided trans alcohol **27b***, which was best converted into cis alcohol **27a*** through oxidation−reduction. This alcohol was then transformed into the dichloroketene cycloaddition substrate **27c***, from which the first synthesis of (−)-homogynolide A

(44) See, for example: Bohlmann, F.; Tietze, B.-M. *Chem. Ber.* **1970**, *103*, 561−563. Hoskins, W. M.; Crout, D. H. G. *J. Chem. Soc., Perkin Trans. I* **1977**, 538−544. Beeby, P. J. *Tetrahedron Lett.* **1977**, 3379−3382. Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2582−2584. Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4056−4068. Nakayama, J.; Nakamura, Y.; Tajiri, T.; Hoshino, M. *Heterocycles* **1986**, *24*, 637−640. Bal-Tembe, S.; Bhedi, D. N.; De Souza, N. J.; Rupp, R. H. *Heterocycles* **1987**, *26*, 1239−1249. Dev, V.; Bottini, A. T. *J. Nat. Prod.* **1987**, *50*, 968−971. Joseph-Nathan, P.; Cerda, C. M.; Roman, L. U.; Hernandez, J. D. *J. Nat. Prod.* **1989**, *52*, 481−496. For relevant studies of the problem of *Z* → *E* isomerization during esterification, see: Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 1772−1783 and 4332−4339.

(45) See: Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. The mixed anhydride formed with trifluoroacetic anhydride has been reported to convert (*E*)-2-methyl-2-butenol to its angelate ester in only 21% yield. See: Rücker, G.; Mayer, R.; Lee, K. R. *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 821−826.

(46) Hartmann, B.; Kanazawa, A.; Deprés, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077−5080.

(47) For the use of carvone in synthesis, see: Ho, T.-L. *Enantioselective Synthesis*; John Wiley-Interscience: New York, 1992; Chapter 6 and references therein.

(48) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601−602.

(49) Posner, G. H. *Org. React.* **1972**, *19*, 1−113.

(50) Criegee, R.; Kaspar, R. *J. Liebigs Ann. Chem.* **1948**, *560*, 127−135. Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 745−752. For some applications, see: Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363−2366. Okamura, W. H.; Aurrecoechea, J.-M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072−4083.

(**2a***) could be achieved by using the chemistry developed for the racemic product.[51] The synthetic (−)-homogynolide A (mp 62−64 °C, CD $\Delta\epsilon_{217}$ −2.50) provided a high-field proton NMR spectrum identical to that of the naturally derived substance (mp[4a] 62−65 °C, CD[4a] $\Delta\epsilon_{220}$ −2.51).

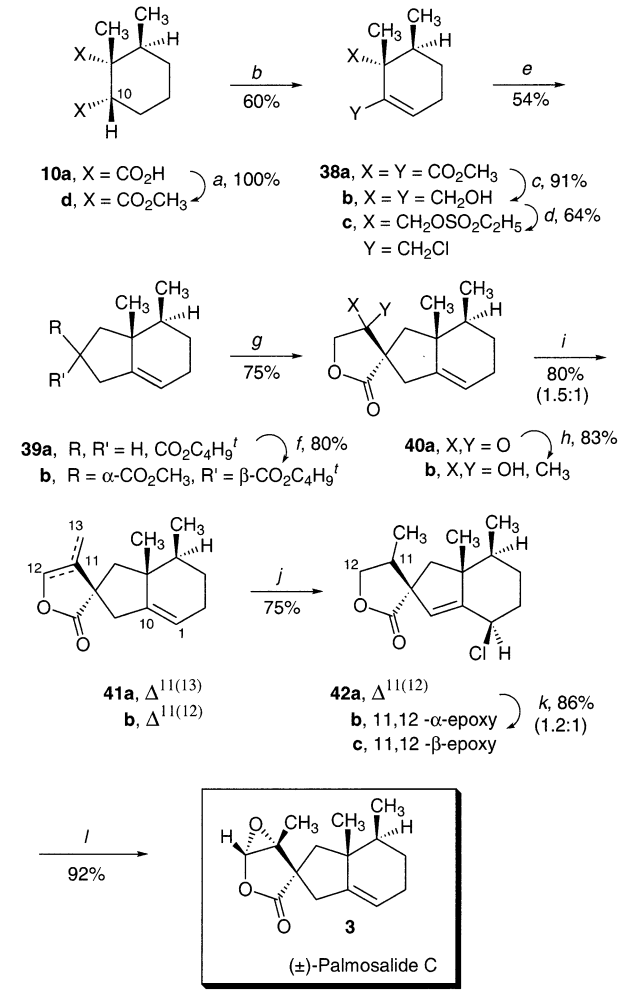
Palmosalide C. The sole reported bakkane of marine origin, palmosalide C (**3**, Chart 1), differs from all of the known terrestial members of this family, except senauricolide,[9] by the presence of the unusual spiro β,γ-epoxy-γ-butyrolactone function, which is found in only a few other sesquiterpenes, such as dysetherin,[52a] ptychanolide,[52b] spirotubipolide,[52c] and spirodensifolins A and B[52d] (none synthesized to date), and through its relative configuration at the C-7 spiro center and unsaturation at C-1,C-10. Palmosalide C was isolated by Fenical and co-workers[5] from the telestacean octocoral *Coelogorgia palmosa*, a rare gorgonian-like soft coral found in the Indian Ocean.

The most difficult synthetic challenge in preparing palmosalide C obviously resides in accessing the epoxy lactone: not only does a procedure that is compatible with the B-ring unsaturation or equivalent have to be found simply for its construction, but, in addition, the issue of stereochemistry at both C-7 and C-11,C-12 needs to be addressed. The latter concern is not necessarily trivial, as demonstrated by Dreiding and co-workers in their failed approach to ptychanolide.[52e]

The $\Delta^{1(10)}$ analogue of a bis-electrophile such as **10c** (Scheme 1) was considered an attractive intermediate for the present synthesis, due, in particular, to its expected accessibility and the many synthetic options it might permit. Thus, diester **10d** (Scheme 6), available in quantitative yield from diacid **10a** by treatment with ethereal diazomethane, was phenylselenenylated[53] at C-10 through reaction with LDA and phenylselenenyl chloride to give the expected selenide, which on exposure to ozone provided the unsaturated diester **38a** in 60% overall yield. Conversion of diester **38a** into diol **38b**, surprisingly, could not be achieved satisfactorily with lithium aluminum hydride in THF or ether or with Dibal-H in THF; Dibal-H in toluene, however, was quite effective and delivered the desired diol in 91% yield.

The transformation of diol **38b** into a useful bis-electrophile was expected to be somewhat challenging because of the increase in reactivity at C-9 (now allylic position) relative to that at C-6 (neopentyl position). Treatment of the bis-trimethylsilyl derivative of diol **38b** with trimethylsilyl iodide,[25] in fact, generated uniquely the tetrahydrofuran (cf. **10b** → **10c**, Scheme 1). Many other attempts were similarly unproductive. Fortunately, however, it was found that the bis-mesylate could be prepared with 5 equiv of methanesulfonyl chloride and 5 equiv of collidine in dichloromethane at 20 °C and that it underwent in situ clean allylic displacement, without rearrangement, with

Scheme 6 [a]



[a] (a) CH_2N_2, $(C_2H_5)_2O$, 20 °C. (b) LDA, THF, HMPA, −78 °C, then C_6H_5SeCl; O_3, CH_2Cl_2, −78 °C, then $(i\text{-}C_3H_7)_2NH$, −78 → 20 °C. (c) DIBAL-H, $C_6H_5CH_3$, 0 °C. (d) $C_2H_5SO_2Cl$, collidine, CH_2Cl_2, 20 °C. (e) $(CH_3)_3CO_2CCH_2CO_2CH_3$, NaH, HMPA, 0 → 20 °C, then NaCN, 110 °C. (f) LDA, $NCCO_2CH_3$, −78 → 20 °C. (g) CF_3CO_2H, CH_2Cl_2, 20 °C, then evaporation, $SOCl_2$, DMF, 60 °C, then evaporation, CH_2N_2, ether, 0 °C, then evaporation, aqueous HCl−CH_3OH, 0 °C. (h) CH_3MgBr, $(C_2H_5)_2O$, 0 °C. (i) $SOCl_2$, C_5H_5N, $C_6H_5CH_3$, 60 °C, separation. (j) **41b**: SO_2Cl_2, $C_6H_5CH_3$, 20 °C. (k) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 20 °C, separation. (l) **42b**: Zn, CH_3CO_2H−$(C_2H_5)_2O$.

the chloride generated during the reaction to give in 70% yield the chloro mesylate (**38c**, SO_2CH_3 replaces $SO_2C_2H_5$).[54] Other reaction conditions led to poorer results, often due to allylic rearrangement. The corresponding bromide could also be prepared by using methanesulfonyl bromide, but the yield was considerably lower than that of the chloride.

With an appropriate bis-electrophile now available, ring closure was first attempted with β-methyl-α,β-butenolide, which, had it been successful, would have swiftly positioned us within striking distance of palmosalide C. Unfortunately, however, none of the desired hydrindane was ever observed. Pattenden and Gedge[55] had earlier observed that alkylation of this lactone with prenyl bromide occurred predominantly at the endocyclic γ

(51) The diiodo alcohol **30a*** was, however, subjected to the Noe acetal technique (91% efficiency) to remove the ca. 8% of enantiomeric material that originated from cis conjugate addition to (+)-carvone. Noe, C. R. *Chem. Ber.* **1982**, *115*, 1591−1606.

(52) (a) Schram, T. J.; Cardellina, J. H., II. *J. Org. Chem.* **1985**, *50*, 4155−4157. (b) Takeda, R.; Naoki, H.; Iwashita, T.; Mizukawa, K.; Hirose, Y.; Isida, T.; Inoue, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1125−1132. (c) Iguchi, K.; Mori, K.; Matsushima, M.; Yamada, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3532−3533. (d) Tori, M.; Arbiyanti, H.; Taira, Z.; Asakawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4011−4012. (e) For the synthesis of a nonnatural spiro β,γ-epoxy-γ-butyrolactone, see: Solaja, B.; Huguet, J.; Karpf, M.; Dreiding, A. S. *Tetrahedron* **1987**, *43*, 4875−4886. For examples of diterpenes with this lactone function, see: Cardenas, J.; Pavon, T.; Esquivel, B.; Toscano, A.; Rodriguez-Hahn, L. *Tetrahedron Lett.* **1992**, *33*, 581−584.

(53) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137−6139. Iodination, followed by treatment with DBU, also yielded **38a**, but less efficiently.

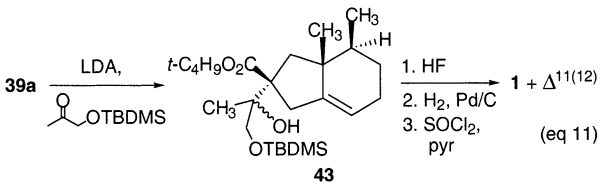
(54) See: Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044−3045. See also: Bishop, C. E.; Morrow, G. W. *J. Org. Chem.* **1983**, *48*, 657−660. Majetich, G.; Song, J. S.; Ringold, C.; Nemeth, G. A.; Newton, M. G. *J. Org. Chem.* **1991**, *56*, 3973−3988.

(55) Pattenden, G.; Gedge, D. R. *Tetrahedron Lett.* **1977**, 4443−4446. The α-carbomethoxy derivative also failed to give satisfactory results.

position. A less direct, but possibly more stereorational, stepwise approach was therefore considered at this stage.

While the lithium anion of *tert*-butyl acetate produced the sultone from the chloro mesylate by abstraction of a sulfonate hydrogen, and the corresponding copper reagent[56] gave a 1:1 mixture of S_N2 and S_N2' adducts, the sodium anion of *tert*-butyl methyl malonate afforded in good yield the desired hydrindane, contaminated however with a small amount of the tetrahydrofuran derivative. The formation of this side product, which stems most likely from malonate attack on sulfur, could be completely suppressed by using the corresponding chloro ethanesulfonate **38c**. Addition of chloro ethanesulfonate **38c** to hexamethylphosphoric triamide containing the sodium anion of *tert*-butyl methyl malonate and sodium hydride, followed by in situ decarbomethoxylation of the resulting malonate (1:1 mixture of C-7 epimers) with sodium cyanide,[57] cleanly yielded ester **39a** in 54% yield.

Although A-ring β-face (convex) approach in the case of saturated bakkane derivatives can be readily predicted from molecular models and has, in fact, been observed,[13,15e] with a $\Delta^{1(10)}$ derivative such as **39a**, the face selectivity to be expected on reaction at C-7 is less obvious because of a flattening of the rings. In an initial approach to palmosalide C, however, ester **39a** on exposure to LDA and then *tert*-butyldimethylsilyloxyacetone was found to yield a mixture of two diastereomeric hydroxy esters that on lactonization, hydrogenation, and dehydration afforded *only* bakkenolide A and its $\Delta^{11(12)}$ isomer (eq 11).[58] α-Face attack is thus clearly preferred in this $\Delta^{1(10)}$



bakkane derivative, which can be attributed a posterori to dominant steric hindrance now by the angular methyl group. While the initial approach was obviously not viable, this clear facial bias pointed to an alternative strategy for the stereoselective construction of the "inverted" lactone of palmosalide C.

Ester **39a** was treated with LDA and then methyl cyanoformate (Mander's reagent[59]) to give in 80% yield a single malonate, presumed to have the stereochemistry indicated in **39b**. In the presence of trifluoroacetic acid, this malonate was converted into an acid ester, which on successive treatment with thionyl chloride, ethereal diazomethane, and hydrochloric acid generated keto lactone **40a**.[60] This one-pot sequence of four steps proceeded in a highly satisfactory 75% overall yield.

The next objective was to convert keto lactone **40a** into the corresponding β-methyl-β,γ-butenolide in anticipation of epoxidation. Unfortunately, the preparation from **40a** of the vinyl iodide,[61a] trimethylsilyl enol ether,[61b] enol phosphate,[61c] or enol triflate[61d] derivative for subsequent methylation could not be effected in an acceptable yield, and therefore the classical Grignard methylation−dehydration procedure was adopted for this transformation. On treatment with methylmagnesium bromide, keto lactone **40a** was smoothly converted into a diastereomeric mixture of tertiary alcohols **40b** (83%),[62] which under optimized dehydration conditions[63] provided an easily separated 1.5:1 mixture of the exo and endo olefins **41a**,**b** (80%). The undesired exo isomer (**41a**) on treatment with osmium tetroxide-sodium periodate readily returned keto lactone **40a** (67% yield) and could thus be recycled.

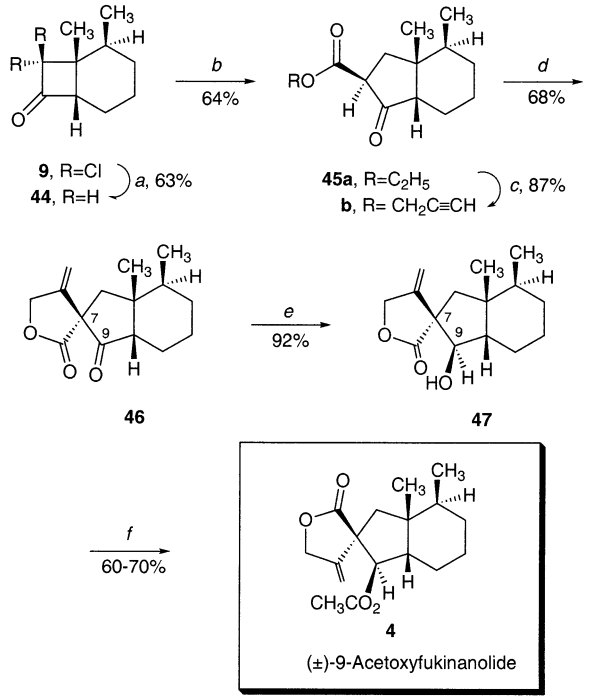
With the long-sought diene **41b** in hand, all that remained was to epoxidize selectively the molecule at C-11,C-12, but this double bond was quickly determined to be the less reactive: both *m*-chloroperbenzoic acid and dimethyldioxirane reacted preferentially at C-1,C-10. Furthermore, the bis-epoxide, formed with an excess of *m*-chloroperbenzoic acid, underwent selective reduction with several reagents at the lactone site. After considerable experimentation, however, a productive protocol for effecting the desired epoxidation was found based on *selective deactivation* of the C-1,C-10 double bond. Treatment of diene **41b** with sulfuryl chloride[64] in the presence of sodium carbonate delivered with total regio- and stereoselectivity allylic chloride **42a** (75% yield), which, precedent suggested,[65] might now undergo selectively butenolide epoxidation. Pleasingly, this, in fact, occurred on exposure to *m*-chloroperbenzoic acid to give a separable 1.2:1 mixture of diastereomeric epoxides **42b**,**c** in 86% yield. The major isomer (**42b**) on treatment with zinc in acetic acid suffered dechlorination with concomitant retransposition of the double bond to give in 92% yield racemic palmosalide C, identified through direct chromatographic and spectroscopic comparison with an authetic sample of the natural product.[66]

This first and, to date, only synthesis of this novel marine bakkane requires 17 steps from diacid **10a**. It proceeds with modest stereochemical control at C-11,C-12, but virtually complete control at the C-4, C-5, and C-7 stereocenters.

9-Acetoxyfukinanolide. While the modified strategy used for palmosalide C could have, in principle, been adapted to provide 9-acetoxyfukinanolide (**4**, Chart 1), it seemed a more expeditious route to this natural product might be available from the same dichloroketene-dimethylcyclohexene cycloadduct **9**

(56) Kuwajima, I.; Doi, Y. *Tetrahedron Lett.* **1972**, 1163−1166.
(57) Müller, P.; Siegfried, B. *Tetrahedron Lett.* **1973**, 3565−3568.
(58) That the C-7 configuration of the $\Delta^{11(12)}$ isomer that corresponded to that of bakkenolide A was demonstrated by hydrogenation of each to a mixture of the same dihydro derivatives.
(59) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.
(60) See: Smith, A. B., III; Dieter, R. K. *Tetrahedron* **1981**, *37*, 2407−2439. Miller, R. D.; Theis, W. *Tetrahedron Lett.* **1987**, *28*, 1039−1042.
(61) (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron Lett.* **1983**, *24*, 1605−1608. Paquette, L. A.; Bellamy, F.; Wells, G. J.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1981**, *103*, 7122−7133. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915−3918. Brownbridge, P. *Synthesis* **1983**, 1−28. (c) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531−2534. Takai, K.; Sato, K.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 108−115. (d) Stang, P. J.; Hanack, M.; Subramaniam, L. R. *Synthesis* **1982**, 85−126. Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47−54. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.
(62) On hydrogenation followed by dehydration, the tertiary alcohols afforded, in addition to the endocyclic olefin, the previously prepared 7-*epi*-bakkenolide A, thereby confirming the presumed C-7 configuration in malonate **39b**.
(63) With 4-hydroxy-4-methyl-2-oxaspiro[4.4]nonan-1-one as a model system, numerous dehydration conditions were examined. With the exception of *p*-TsOH in refluxing toluene (only endo, yield < 30%), $SOCl_2$ in pyridine at 60 °C gave the best endo/exo ratio (1/1.2).
(64) Poutsma, M. L. *J. Am. Chem. Soc.* **1965**, *87*, 4285−4293. Bulliard, M.; Balme, G.; Goré, J. *Tetrahedron Lett.* **1989**, *30*, 5767−5770. Chlorine or iodobenzene dichloride could also be used for this purpose. For other examples of ene-type chlorination, see: Rodriguez, J.; Dulcère, J.-P. *Synlett* **1991**, 477−478 and references therein.
(65) Williard, P. G.; de Laszlo, S. E. *J. Org. Chem.* **1985**, *50*, 3738−3749. Selective formation of a dibromo (or similar) derivative for double bond protection could not be achieved.
(66) The minor epoxide isomer (**42c**) on similar treatment produced material distinctly different from the natural product.

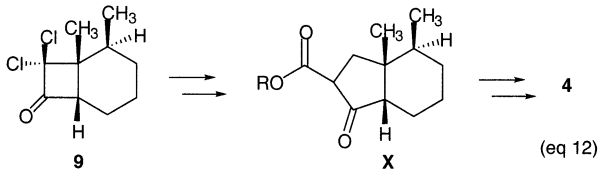
Scheme 7 [a]



[a] (a) Zn, CH_3CO_2H, 70 °C, 3 h. (b) $N_2CHCO_2C_2H_5$, $SbCl_5$, CH_2Cl_2, −78 → −30 °C, 12 h. (c) $HOCH_2C{\equiv}CH$, $C_6H_5CH_3$, Δ. (d) $Mn(O_2CCH_3)_3$, C_2H_5OH, 20 °C. (e) SmI_2, $THF-H_2O$, 20 °C. (f) TBAF, THF, 0 °C; CH_3COCl, $(C_2H_5)_3N$, DMAP, THF, 20 °C.

(Scheme 7). 9-Acetoxyfukinanolide (9-acetoxybakkenolide A), isolated by Naya and co-workers from the leaves of *Petasites japonicus* Maxim in 1972,[6] was targeted with the expectation that the chemistry developed might later be extrapolated to allow access to the most synthetically challenging and numerous bakkenolides, those oxygenated at C-1 and at C-9 (e.g., **5a**−**i**, Chart 1**)**.

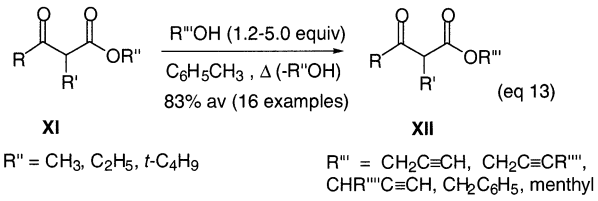
The approach that was conceived called for a regioselective cyclobutanone ring expansion of **9** to provide **X**, which would be the platform for constructing the β-methylene-γ-butyrolactone intermediate that would then be converted into 9-acetoxyfukinanolide (**4**) (eq 12).[67]



The cycloadduct was dechlorinated with zinc in warm acetic acid to give cyclobutanone **44** (Scheme 7), which underwent regioselective ring expansion (84:16) in the expected sense in the presence of ethyl diazoacetate and antimony pentachloride[68] to provide the β-keto ester **45a** as a single isomer in 64% yield after purification. It was hoped at this point that it might be possible to use the β-hydroxy ester from **45a** for lactone construction in a way parallel to that shown in eq 11. This approach had to be abandoned, however, because of the difficulty encountered in stereoselectively reducing β-keto ester **45a** and, additionally, in effecting the desired condensation in a closely related model system.

In 1989, Cossy and Leblanc disclosed[69] an effective spiro β-methylene-γ-butyrolactam synthesis based on free-radical cyclization of *N*-propargyl β-keto amides with manganese triacetate[70] in ethanol. This type of approach seemed worth investigating because propargylic β-keto esters could reasonably be expected to behave similarly. The report by Bertrand and co-workers[71] that an ethyl propargyl malonate also cyclized in the presence of manganese triacetate allowed us to be optimistic.

A search of the literature, however, failed to reveal any pertinent examples of transesterification of a β-keto ester with a propargylic alcohol, and, in fact, attempts using conventional procedures led, in our hands, to generally poor results.[72] After some study, though, it was discovered that by simply displacing the equilibrium *without catalysis*, propargylic β-keto esters could be readily prepared from methyl, ethyl, and *tert*-butyl β-keto esters with primary and secondary propargylic alcohols.[73] Most likely proceeding through a ketene intermediate, this exceedingly simple, yet effective, method could also be applied to a large range of nonpropargylic alcohols with results generally far superior to those in the literature (eq 13). Applied to the problem at hand, the desired propargyl β-keto ester **45b** was secured in 87% yield.[74]



With the requisite keto ester available, the crucial spiro β-methylene-γ-lactonization was next attempted. Pleasingly, in the presence of 2.5 equiv of manganese triacetate in deoxygenated ethanol at 20 °C, **45b** cleanly underwent 5-*exo dig* cyclization to provide in 68% yield a single lactone (**46**).

It is noteworthy that recent work has revealed the generality of the spiro β-methylene-γ-lactonization reaction leading to **46** (Table 1). As can be seen in the table, the free-radical cyclization

(67) In an earlier approach based on the cycloalkylation of acrylate **13** with **10c**, in which a formyl or a chloroformyl group replaces the C-10 (bakkane numbering) iodomethyl, only the formation of the undesired tetrahydrofuran derivatives from internal alkylation on oxygen was observed regardless of the experimental conditions.

(68) Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, 4937−4940. Sonawane, H. R.; Nanjundiah, B. S.; Shah, V. G.; Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron Lett.* **1991**, *32*, 1107−1108. See also: Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459−465 and 466−472. Boron trifluoride etherate has also been used in this reaction.[14i]

(69) Cossy, J.; Leblanc, C. *Tetrahedron Lett.* **1989**, *30*, 4531−4534. Cossy, J.; Bouzide, A.; Leblanc, C. *J. Org. Chem.* **2000**, *65*, 7257−7265.

(70) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363 and references therein.

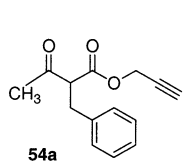
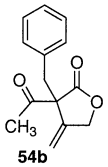
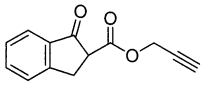
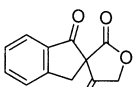
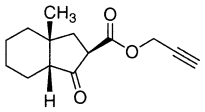
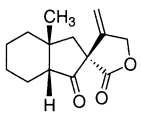
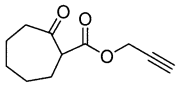
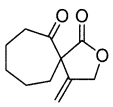
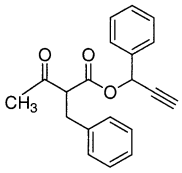
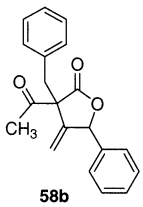
(71) Oumar-Mahamat, H.; Moustrou, C.; Surzur, J. M.; Bertrand, M. P. *J. Org. Chem.* **1989**, *54*, 5684−5688. For a catalytic approach, see: Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970−973. For related protocols for effecting free-radical spiro lactonization, see: Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806−3814 and ref 76. See also: Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Keller, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 11275−11286. For a review of the various methods for preparing β-methylene-γ-butyrolactones, see ref 1b.

(72) For a review on transesterification, see: Otera, J. *Chem. Rev.* **1993**, *93*, 1449−1470.

(73) Mottet, C.; Hamelin, O.; Garavel, G. D.; Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380−1382. For the basis of this work, see: Bader, A. R.; Cummings, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, *73*, 4195−4197. Bader, A. R.; Vogel, H. A. *J. Am. Chem. Soc.* **1952**, *74*, 3992−3994. For a mechanistic study, see: Campbell, D. S.; Lawrie, C. W. *J. Chem. Soc., Chem. Commun.* **1971**, 355−356.

(74) Initially, the β-keto ester was refluxed in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid and with slow distillation; however, the present method has been found much superior.

Table 1. Synthesis of Spiro-fused β-Methylene-γ-lactones from Propargylic β-Keto Esters[a]

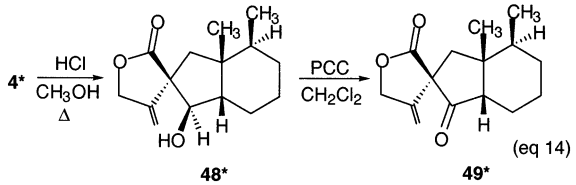
Entry	Keto Ester	Lactone	Yield[b]
1.	 **54a**	 **54b**	50%
2.	 **55a**	 **55b**	52%
3.	 **56a**	 **56b**	75%[c]
4.	 **57a**	 **57b**	52%
5.	 **58a**	 **58b**	38%[d]

[a] $Mn(O_2CCH_3)_3 \cdot 2H_2O$ (ca. 2.4 equiv) in deoxygenated C_2H_5OH, 20 °C, 14 h. [b] Yields are for pure, homogeneous products (except for **58b**). [c] Relative configuration determined by X-ray crystallography. See ref 75. [d] 2:1 mixture of diastereomers.

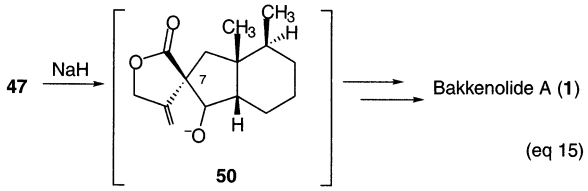
of various acyclic as well as cyclic propargylic β-keto esters results in synthetically useful yields of the corresponding β-methylene-γ-lactones, even when a reactive benzylic site (entries 1,2) is present in the substrate. An encumbering propargylic substituent, however, has a detrimental effect on the yield (entry 1 vs entry 5). This procedure offers a direct route to these polyfunctional compounds[1b] and should find additional application.

Unfortunately, NMR and molecular modeling studies with lactone **46** were ambiguous, and the results of Srikrishna and co-workers[76] in related cyclizations were not sufficiently consistent to allow us to assign with confidence the C-7 configuration. Nevertheless, because this keto lactone represented, potentially, the penultimate intermediate in our synthesis, the reduction and acetylation reactions were studied despite the stereochemical uncertainty. While hydride reducting agents, such as $NaBH_4$, $BH_3 \cdot NH_3$, and Dibal-H, reduced selectively the lactone function, SmI_2[77] in 2% aqueous THF at 20 °C afforded a unique hydroxy lactone (**47**) in 92% yield.[78] Acetylation of this substance, however, failed to yield 9-acetoxyfukinanolide, but did provide material with spectroscopic data closely similar to those described for the natural product. To ascertain the configuration at C-7, Barton deoxygenation (NaH, CS_2, CH_3I; $(C_4H_9)_3SnH$)[79] was carried out on the hydroxy lactone (**47**) to eliminate the stereocenter at C-9. This, pleasingly, indeed afforded bakkenolide A (**1**), which seemed to indicate unequivocally that the stereochemical problem lay simply at C-9.

At this crucial point in our work, an authentic sample of the natural product was, fortunately, finally secured from Japan. Acid hydrolysis of this material provided alcohol **48***, which was, as expected, different from our synthetic intermediate (**47**) (eq 14). What was initially puzzling, though, was that the



corresponding ketones (**49*** and **46**) were also different! A logical explanation was soon found, however: a C-7,C-9 retro aldol−aldol epimerization must have taken place in the Barton sequence during xanthate formation, effectively transforming the unnatural C-7 configuration into the natural, hence the conversion into bakkenolide A (eq 15). That this interpretation



was, in fact, correct was established on treatment of alcohol **47** with sodium hydride, which quickly generated a unique product, alcohol **48**.[80]

Molecular mechanics calculations performed on the four possible C-7,C-9 diastereomers revealed, as now expected, this alcohol, with the natural relative stereochemistry, to be of lowest energy, followed by **47**.[81] It does not seem unreasonable to assume that the formation of 9-acetoxyfukinanolide in nature involves a similar retro aldol−aldol equilibration for adjusting the stereochemistry at these two vicinal stereocenters.

This fortuitous discovery provided a straightforward dénouement for the synthesis. Exposure of alcohol **47** (Scheme 7) to base, optimally tetrabutylammonium fluoride (TBAF), and in situ acetylation of the resulting equilibrated material gave directly and in good yield racemic 9-acetoxyfukinanolide,

(75) Crystal data for (±)-**56b**: $C_{14}O_3H_{18}$, monoclinic, *C*2/*c*, a = 8.314(3) Å, b = 10.297(5) Å, c = 29.384(8) Å, β = 90.729(3)°, V = 2515(1) Å^3, Z = 8, d_{calcd} = 1.237 mg/m^3, $F(000)$ = 1008.0, Θ_{max} range 2.08−29.96°, 5604 measured reflections, 3877 [R(int) = 0.03610] independent reflections, R(1) [$1 > 2\sigma(I)$] = 0.0482, wR2 [all data] = 0.592, GOF (all data) = 1.967.

(76) Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun.* **1993**, 285−288 and refs 15a−d,f.

(77) For reviews, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. Molander, G. A. *Org. React.* **1994**, *46*, 211−367. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745−777. For a similar reduction problem and an alternative solution, see: Wang, T.-Z.; Pinard, E.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 1309−1318.

(78) NMR experiments for the purpose of assigning stereochemistry again were not unequivocable.

(79) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. Hartwig, W. *Tetrahedron* **1983**, *39*, 2609−2645.

(80) For a related example, see: White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. *J. Am. Chem. Soc.* **1995**, *117*, 9780−9781.

(81) Molecular modeling was performed on a Silicon Graphics MD25G workstation running Insight II Discover, version 2.3.0 (Biosym Technologies, San Diego). The structures were energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. Diastereomer **48**, 39.4 kcal/mol; **47**, 40.5 kcal/mol; 9-*epi*-**48**, 41.7 kcal/mol; 7-*epi*,9-*epi*-**48**, 42.3 kcal/mol.

identical except for rotation and melting point with the natural sample. Single-crystal X-ray analyses[14g] of hydroxy lactone **47** (dichloroacetate derivative) and the racemic natural product subsequently confirmed the stereochemical evolution over the course of this first total synthesis.

The preparation of 9-acetoxyfukanolide could thus be accomplished in seven steps and 15% overall yield from dimethylcyclohexene **8** and with virtually complete stereochemical control. By substituting enantiopure (*S*)-1,6-dimethyl-1-cyclohexene (**8***) for **8**, the natural product itself could be similarly obtained (mp 93 °C, $[\alpha]^{25}_D$ −28.6; lit.[6] 96−97 °C, $[\alpha]^{25}_D$ −28.5).

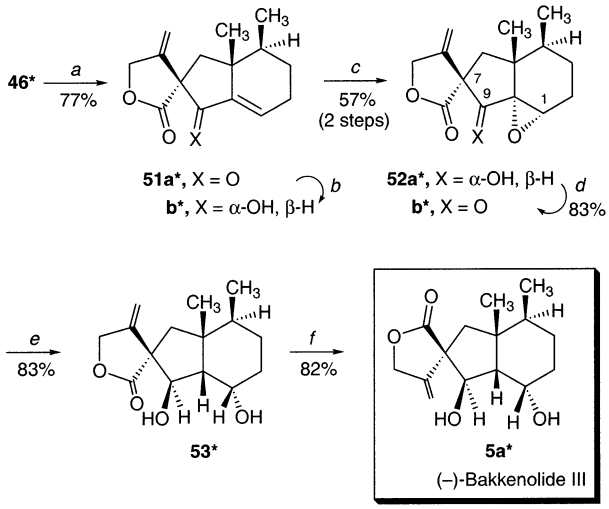
Bakkenolides III, B, C, H, L, V, and X. No approach to the bakkanes could be considered general without providing an entry to the numerous C-1,C-9 dioxygenated bakkenolides. These densely functionalized, synthetically challenging lactones, isolated from *Petasites japonicus* Maxim and *Petasites formosanus* Kitamura (Compositae),[3b,c,7a,b,8] possess significant inhibitory activity toward Hep G2, Hep G2,2,15, and P-388 tumor cell lines[8b] and PAF, arachidonic acid, and collagen-induced platelet aggregation.[8a] The keto lactone **46*** from the previous synthesis appeared to offer various possibilities toward this end, but in all of them, dehydrogenation to the $\Delta^{1(10)}$ derivative seemed essential.

The trimethylsilyl enol ether of **46*** could be formed cleanly with trimethylsilyl chloride and triethylamine in warm DMF, but in the presence of palladium acetate,[82] it afforded only a low yield of the desired enone, the remainder of the material being the starting ketone **46***. Fortunately, the obvious alternative of phenylselenenylation-oxidative elimination[83] proceeded smoothly to deliver the dehydro derivative **51a*** in 77% yield (Scheme 8).

Because direct, base-catalyzed epoxidation led to total destruction of the molecule, a three-step protocol for transforming enone **51a*** to the corresponding epoxy ketone was examined, with the hope that the α isomer **52b*** would be produced. This epoxy ketone was viewed as a potentially useful compound for accessing the C-1α,C-9β (or α) diol, which, once in hand, could be subjected to C-7,C-9 stereochemical equilibration through the previously used retro aldol−aldol reaction to obtain the lowest-energy isomer, (−)-bakkenolide III (**5a***), the envisaged pivotal synthetic intermediate.[84]

On the basis of a chelation model[85] and literature precedent,[13,15e] it appeared that Luche reduction[48] of enone **51a*** might selectively generate the desired α-hydroxyl, which would be well-positioned to direct the epoxidation to the same face of the allylic system in the presence of the homoallylic system. Oxidation of the resulting epoxy alcohol would then restore the carbonyl function and give epoxy ketone **52b***. To our delight, this scenario, in reality, played out as planned: Luche reduction of enone **51a*** in ethanol provided highly stereoselectively (≥98%) the retro aldol-prone[86] allylic alcohol **51b***, which on

Scheme 8 [a]



[a] (a) NaHMDS, THF, −65 °C; C_6H_5SeBr, −65 → 0 °C; H_2O_2, $CH_3CO_2H-H_2O$, 0 °C. (b) $NaBH_4$, $CeCl_3$, C_2H_5OH, −30 °C. (c) $VO(acac)_2$, TBHP, $C_6H_5CH_3$, 50−60 °C. (d) $(ClCO)_2$, DMSO, CH_2Cl_2, −60 °C; $(C_2H_5)_3N$, −60 → 20 °C. (e) SmI_2, THF−H_2O, 20 °C. (f) $(C_4H_9)_4NF$, THF, 0 °C.

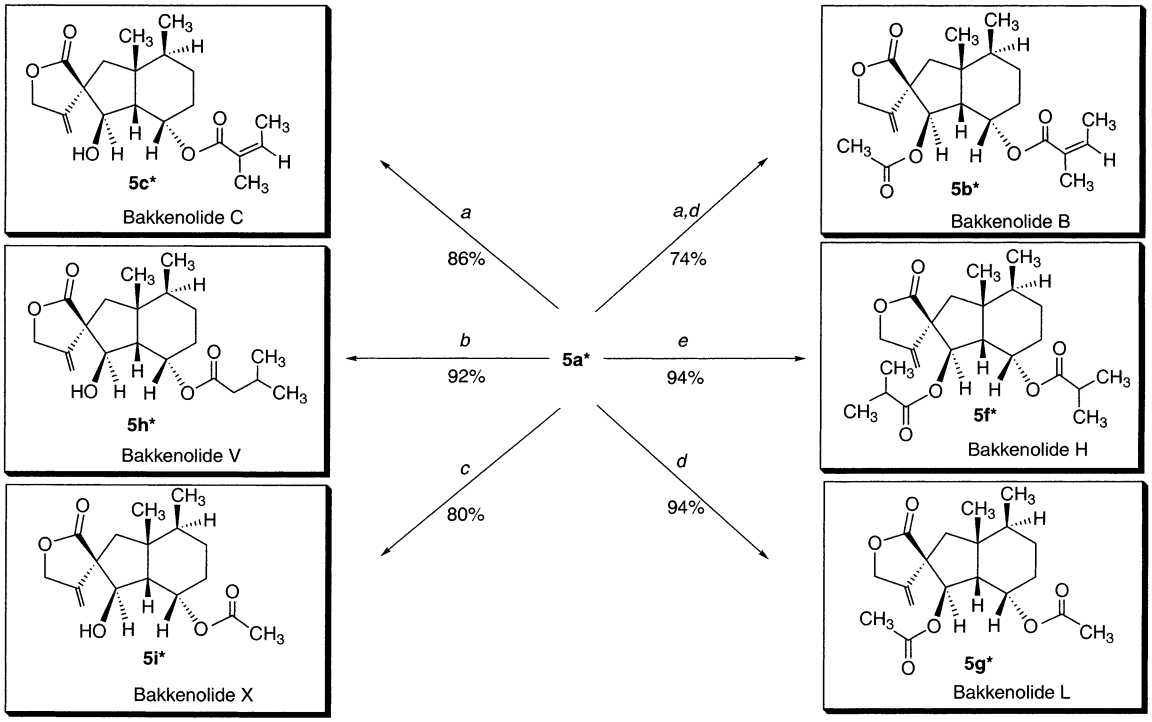
$[VO(acac)_2]$-catalyzed epoxidation with *tert*-butyl hydroperoxide[87] (57%, two steps) and Swern oxidation (83%) afforded epoxy ketone **52b*** via epoxy alcohol **52a***. While the stereochemical assignments were at this point tentative, they were soon confirmed.

Samarium(II) iodide was known to both effectively cleave α heteroatom substituents in ketone derivatives and reduce ketones,[77] and thus it was surprising to find that these two transformations had not previously been coupled for producing 1,3-diols from epoxy ketones. Because Birch conditions, known[88] to be capable of effecting this type of conversion, lacked the necessary chemoselectivity, the possibility of using samarium diiodide as an alternative was examined in some detail. It was eventually found that in the presence of excess reagent in 1% aqueous THF at 20 °C for 0.5 h, epoxy ketone **52b*** suffered clean, chemoselective double reduction to generate a unique diol (**53***) in 83% yield. This diol was initially assigned the C-1α,C-9β configurations on the basis of the above considerations and because samarium diiodide was known to produce, generally, the more stable[84] isomer (e.g., **46** → **47**,[81] Scheme 7); a single-crystal X-ray analysis[14i] offered, nonetheless, most welcome confirmation. Only the C-1 configuration is relevant at this point, however.

The crucial retro aldol−aldol reaction for correcting the C-7 stereocenter was next investigated. To our utter delight, diol **53*** on exposure to TBAF in THF at 0 °C for 0.5 h did indeed smoothly isomerize as predicted to the lowest energy[84] C-7,C-9 isomer, notwithstanding the complexity of the system and the alternative pathways that might attend such a transformation. That the crystalline product, formed in 82% yield, was, in fact, (−)-bakkenolide III (**5a***)[8b] was initially shown through direct comparison with the hydrolysis product[3c,d,7a] of (−)-bakkenolide B and then confirmed by single-crystal X-ray analysis.[14i]

(82) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.
(83) For a review, see: Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1−296.
(84) Calculations were performed on an IBM RS 6000 workstation running Insight II Discover 98.0 (MSI, San Diego). The structures were energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. Diastereomer **5a***, 39.2 kcal/mol; **53***, 40.0 kcal/mol; 7-*epi*,9-*epi*-**5a***, 42.0 kcal/mol; 9-*epi*-**5a***, 44.3 kcal/mol.
(85) Cf.: Krief, A.; Surleraux, D.; Ropson, N. *Tetrahedron: Asymmetry* **1993**, *4*, 289−292.
(86) For a closely related (postulated) example in mass spectrometry, see ref 3b.
(87) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159−169. For reviews, see: Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−74. Jørgensen, K. A. *Chem. Rev.* **1989**, *89*, 431−458.
(88) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3039−3048. Swindell, C. S.; deSolms, S. J. *Tetrahedron Lett.* **1984**, *25*, 3801−3804.

Scheme 9 [a]



[a] (a) (*Z*)-2,4,6-$Cl_3C_6H_2CO_2COC(CH_3)$═$CHCH_3$, $C_6H_5CH_3$, Δ. (b) $(CH_3)_2CHCH_2CO)_2O$, C_5H_5N, $C_6H_5CH_3$, 20 °C. (c) $(CH_3CO)_2O$, C_5H_5N, $C_6H_5CH_3$, 20 °C. (d) $(CH_3CO)_2O$, C_5H_5N, DMAP, 20 °C. (e) $((CH_3)_2CHCO)_2O$, C_5H_5N, DMAP, 20 °C.

(−)-Bakkenolide III, with its two hydroxyl groups in quite different steric environments, *is the ideal platform for accessing the entire range of C-1,C-9-difunctionalized bakkenolides*. To illustrate this point, the representative bakkenolides B, C, and H, and, quite recently, L, V, and X, have been prepared (Scheme 9). The angelic ester, (−)-bakkenolide C (**5c***),[3c,d,7a] was readily synthesized in 86% yield by using the Yamaguchi mixed anhydride under our earlier developed conditions (see eq 9), to the complete exclusion of tiglic ester and diacylated material. The mono esters (−)-bakkenolide V (**5h***)[8b] and (−)-bakkenolide X (**5i***)[8b] could also be secured highly selectively and in good yield with isovaleryl anhydride and acetic anhydride, respectively. The diesters (−)-bakkenolide B (**5b***)[3c,d,7a,8b] and (−)-bakkenolide L (**5g***)[8b] were easily obtained from (−)-bakkenolide C and (−)-bakkenolide III, however, with excess acetic anhydride in the presence of DMAP. Similarly, the diisobutyrate (−)-bakkenolide H (**5f***),[8] which shows significant cytotoxic activity in several different systems, could be secured directly from (−)-bakkenolide III in 94% yield through exposure to excess isobutyric anhydride and DMAP.

The synthesis of the naturally occurring bakkanes (−)-bakkenolides III, B, C, H, L, V, and X could thus be accomplished in high yield and with virtually complete stereoselectivity from an efficiently prepared intermediate, keto lactone **46***. The key, thermodynamically driven adjustment of stereochemistry integrated into the approach is especially noteworthy.

Conclusion

A simple, yet highly effective, [2 + 2] cycloaddition reaction of dichloroketene with dimethylcyclohexenes has been exploited for the development of the first comprehensive approach to the bakkanes. The ability of the approach to reach the complex members of the family is seen in the efficient syntheses of the compact, densely functionalized bakkenolides III, B, C, H, L, V, and X.

A number of new and practical methods have resulted from this work. These include (1) spiro β-methylene-γ-butyrolactonization procedures, (2) a vicinal dicarboxylation, (3) an angelic ester preparation, (4) a transesterification protocol, (5) an epoxy ketone double reduction, and (6) a retro aldol−aldol approach to low-energy aldol isomers. Natural product synthesis has thus once again proven an excellent vehicle for the development of new synthetic methodologies. Those above should find additional application.

Acknowledgment. This paper is dedicated with appreciation to Professor Jean Lhomme for his scientific and administrative contributions to the chemistry in Grenoble. We thank Profs. J. Lhomme, G. Mehta, and A. Rassat and Drs. A. Gadras and J.-L. Luche for their interest in our work, Dr. I. Gautier-Luneau and Prof. P. Sinaÿ for fruitful discussions, and Profs. F. Bohlmann, W. Fenical, T. Kato, M. Kawai, and M. Noda, Dr. J. Harmatha, Ms. N. Pujol, and Mr. K. Watanabe for invaluable samples and spectra. In addition, we are indebted to Ms. M.-L. Dheu-Andries and Dr. P. Vatton for their assistance with the molecular modeling, Drs. M.-T. Averbuch, J.-P. Declercq, A. Durif, C. Philouze, and B. Tinant for the X-ray structure determinations, and Mr. F. Bargiggia, Mr. M. Cook, Ms. G. Garavel, Ms. S. Heidenhain, and Mr. C. Mottet for helpful experimental work. We also gratefully acknowledge financial support from the Université Joseph Fourier and the CNRS (UMR 5616) and from Rhône-Poulenc Agro and fellowship awards from the MESR (to O.H.), the CNPq (to F.C., A.M.K, and M.E.F.de L.), and Rhône-Poulenc Agro (to B.H.).

Supporting Information Available: Experimental details and characterization data for the syntheses of **1**, **1***, **2a**, **2a***, **2b***, **3**, **4**, **4***, **5a**−**c***, **5f**−**i***, **54b**−**58b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0208456