Synthetic studies towards bruceantin. Part 2. The synthesis of a pentacyclic intermediate

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In a synthetic approach to the quassinoid bruceantin (**2**), the key intermediate **8** obtained via alkylation of a dianion has been transformed into the pentacyclic intermediate **33** via an ABDC ring forming strategy. The key steps involved in this route are as follows: a unique acid catalyzed cyclization, **19** → **20**; an intramolecular Michael reaction, **24** → **28**; and an allyl sulfoxide [2,3]-sigmatropic rearrangement to introduce the axial C12 alcohol, **31** → **33**.

Key words: bruceantin, quassinoids, cyclization, sulfoxides, sigmatropic rearrangement.

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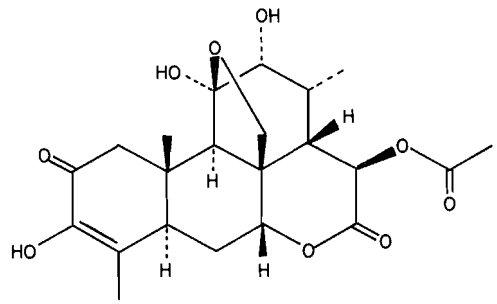
Dans une approche à la synthèse de la quassinoïde brucéantine (**2**), on a transformé l'intermédiaire clé (**8**), obtenu par alkylation d'un dianion, en intermédiaire pentacyclique **33** par le biais de la stratégie de formation des cycles ABDC. Les étapes clés impliquées dans cette voie sont : une cyclisation acido-catalysée unique de **19** en **20**, une réaction de Michael intramoléculaire de **24** en **28** et une transposition sigmatropique-[2,3] d'un sulfoxyde d'allyle pour introduire l'alcool axial en C12, **31** à **33**.

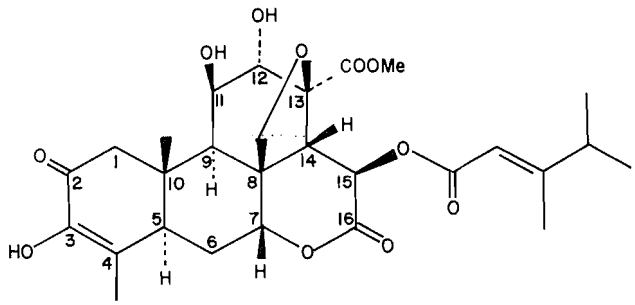
Mots clés : brucéantine, quassinoïde, cyclisation, sulfoxydes, transposition sigmatropique.

[Traduit par la rédaction]

Certain species of the *Simaroubaceae* family have traditionally been used as ingredients for the treatment of dysentery, amebiasis, and other ailments in folk medicine. However, increased attention developed with the report of antileukemic activity of holacanthone **1** (1–3). Since that report bruceantin **2**, a member of the same family, has undergone phase II testing

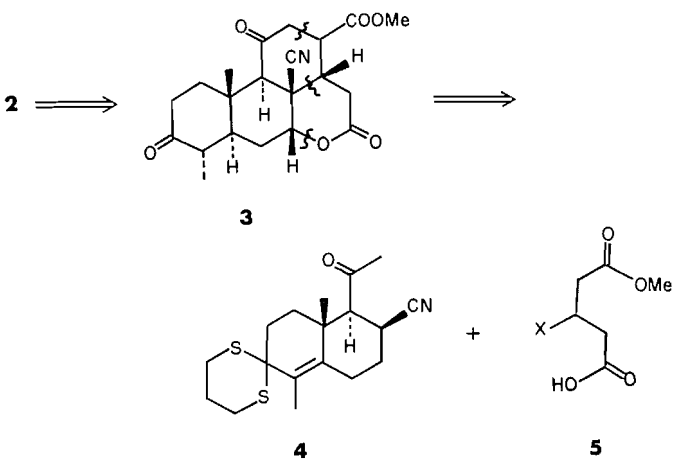


1 Holacanthone



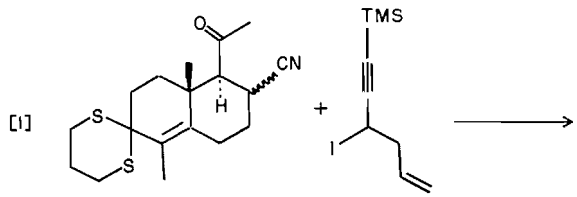
2 Bruceantin

in the United States (4). Due to this biological activity, as well as the fundamental complexity, these compounds have received considerable synthetic attention (5). In the preceding paper (6), we outlined a simple strategy, shown in Scheme 1, which should allow a rapid construction of the quassinoid skeleton, and described a convergent method for the preparation of intermediate **8**, which included the alkylation of the mixture

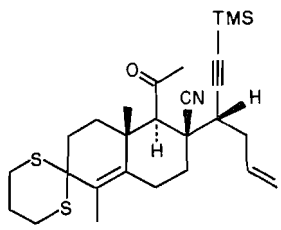


SCHEME 1

of C8-epimers **4** and **6** as the key step (eq. [1]). We now wish to report on the elaboration of this compound into a key pentacyclic intermediate that contains the complete bruceantin skeleton, as well as seven of its 10 chiral centers.



4 + **6** **7**



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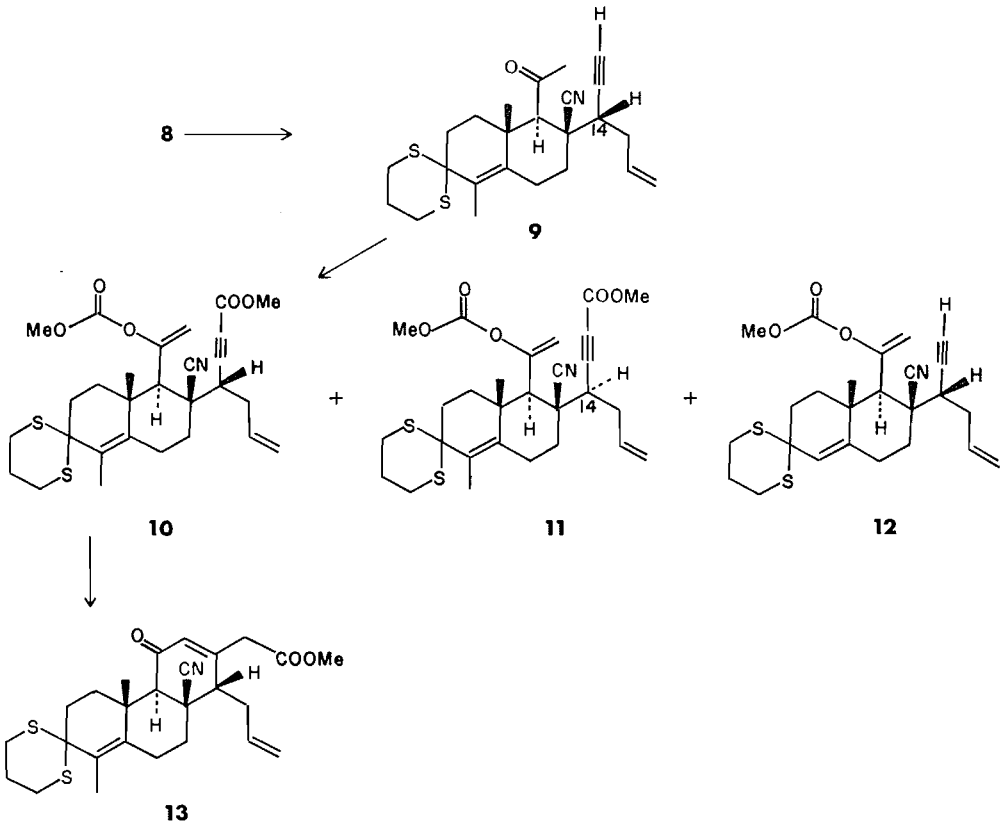


SCHEME 2

Results and discussion

The transformation of intermediate **8** into a compound of type **3** requires that the acetylene functionality be used for the construction of ring C, and that the side-chain double bond be utilized for the formation of lactone ring D. Formation of ring C was envisaged as arising from a simple three-step protocol: deprotection of the acetylene, carbomethoxylation, and an intramolecular Michael reaction. Oxidative cleavage of the olefin would then furnish the carboxylic acid required for lactone formation.

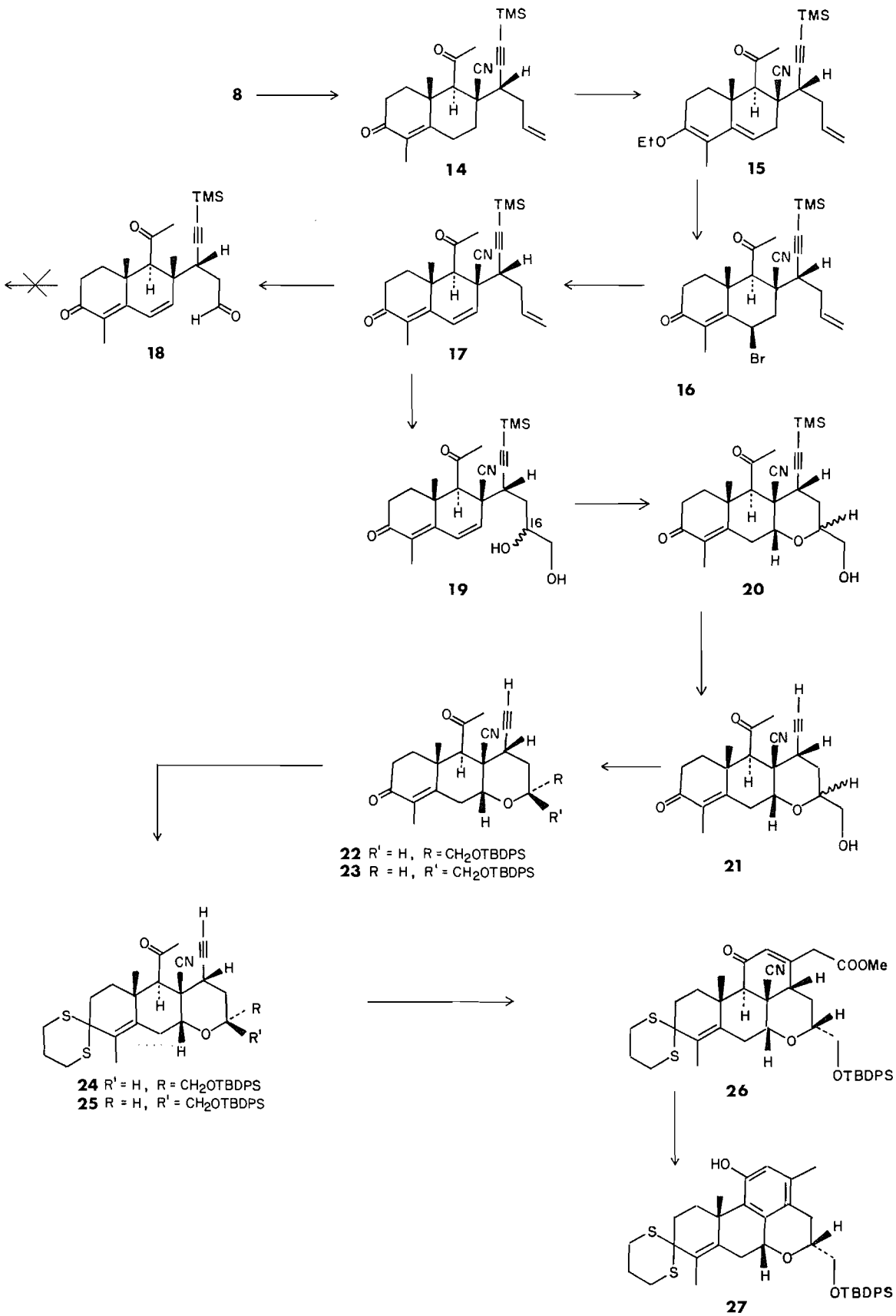
Development of this strategy began with treatment of **8** with tetrabutylammonium fluoride (7) in tetrahydrofuran (THF) to give acetylene **9** in good yield (82%) (Scheme 2). Reaction of the dianion of **9** (*n*BuLi in THF at −78°C) with methyl chloroformate furnished **10**, **11**, and **12** in a 2:1:1 ratio and a 65% combined yield. Conversion of carbonate **10** into ester **13** then proceeded smoothly on treatment with sodium methoxide in THF (25% from **9**). Although the strategy worked, the low yield coupled with 25% epimerization at C14 made this route unattractive. Concerning the epimerization, examination of molecular models revealed that a facile proton shift was possible from C14 to the proximate enolate anion after carbomethoxylation of the acetylene, and that reprotonation of the C14 anion would then occur preferably from the α-side. Constructing ring D first would clearly remedy this problem since the C14 proton could no longer be aligned for the intramolecular proton transfer.

This modified route began with the extension of ring-A conjugation into ring B (Scheme 3). Deprotection of the C3 ketone with mercuric oxide (8) in aqueous THF with a catalytic amount of acid gave enone **14** in quantitative yield. Treatment of **14** with trimethyl orthoformate (9) and a catalytic amount of *p*-toluenesulfonic acid in benzene afforded dienol ether **15** (89%), which was brominated with pyridinium bromide perbromide (10) in aqueous THF to deliver **16** as a single isomer (88%). The exclusive formation of the isomer with an axial bromine at C6 can only be attributed to a strong stereoelectronic effect (11). Efficient dehydrobromination to **17** was then achieved with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in THF (78%). It was found that a significant reduction in yield occurred when the base was not used in large excess and when reaction times exceeded 20 min.

Our next objective was the conversion of the side-chain alkene to a suitably oxygenated derivative. Oxidation of **17** with sodium periodate and a catalytic amount of osmium tetroxide (12) in aqueous ether afforded aldehyde **18** in 73% yield. However, all attempts to oxidize **18** efficiently to the acid failed (PCC, PDC, and MnO_2). Direct oxidation of the olefin to the acid also met with no success. Fortunately, a regioselective incorporation of the diol proceeded with ease, on treatment of **17** under the conditions described by Van Rheenan *et al.* (13), to produce **19** as a mixture of the two C16 epimers (see below) in 84% yield.[2]

Initial attempts to effect cyclization of ring D with a variety of acids proved fruitless. For example, **19** was inert to *p*-toluenesulfonic acid, boron trifluoride etherate, Amberlyst-15 (14), and perchloric acid. However, when **19** was heated with 1,3-propane diol in benzene with one-half equivalent of *p*-toluenesulfonic acid and azeotropic removal of water, 15% of enone **20** was obtained, along with 85% of recovered starting material. *There were no traces of any dioxolane compounds,*

[2]In contrast, an unmediated oxidation with osmium tetroxide alone gave a lower yield of **19** and by-products containing carbonyl groups in the side chain.



SCHEME 3

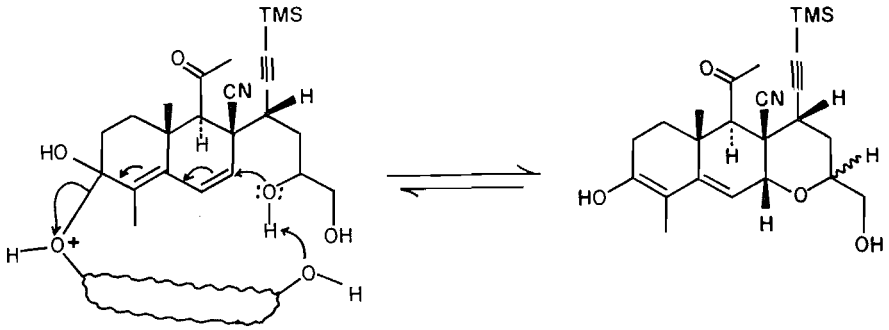


FIG. 1

and under prolonged heating only destruction of starting material was observed. The only difference from previous reaction conditions was the addition of 1,3-propane diol. Therefore, it was postulated that the reaction takes place on the surface of the propane diol[3] in a two-phase reaction (Fig. 1). In one possible interpretation, as part of the surface promotes formation of the oxonium ion at C3, another part of the surface abstracts a proton from the charged ether oxygen before reversion to the open form can occur. Subsequent protonation at C6 can then similarly take place on the surface of protonated propane diol. After considerable experimentation, it was found that **20** (mixture of C16 epimers) could be obtained in 90% yield, based on 20% recovered starting material, by treating diol **19** with 60 equivalents of 1,3-propane diol and 30 equivalents of *p*-toluenesulfonic acid in benzene at 40°C for 4 h. The ^{1}H NMR signal corresponding to C7-H in **20** (δ 4.21, t, J = 3 Hz) showed clearly that the ether O-atom had the desired axial configuration relative to ring B.

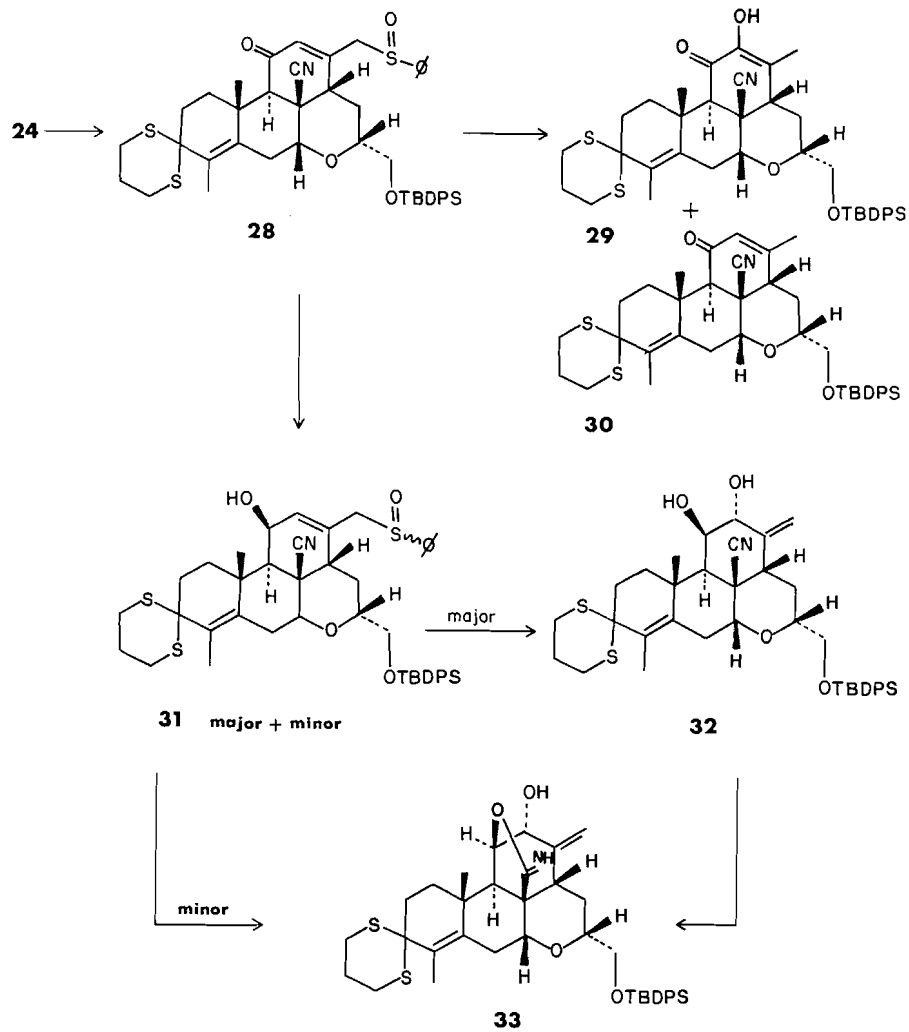
With rings A, B, and D now established, the final task was to incorporate ring C via our previous cyclization protocol. This began by deprotection of acetylene **20** with tetrabutylammonium chloride and potassium fluoride in acetonitrile (15) to deliver **21** in a quantitative yield. Protection of the primary alcohol in **21** with *tert*-butyldiphenylsilyl (TBDPS) chloride and imidazole in dimethylformamide (DMF) (16) then gave a 6:1 mixture of products **22** and **23** in 84% yield. These could be cleanly separated by silica gel chromatography, the ^{1}H NMR spectra showing the predominance of **22** containing the -CH_2OTBDPS group in an equatorial position. The C3 ketone of **22** and **23** was protected as its 1,3-propane dithiane with 1,3-propane dithiol in THF (1:1) at room temperature to provide **24** and **25** in 96 and 84% yield, respectively. The major isomer **24** was then subjected to dianion formation with lithium hexamethyl disilazide in THF at −30°C, followed by a dimethyl carbonate quench to deliver ester **26** in 75% yield. Unfortunately, all attempts to modify this intermediate failed. For example, **26** was inert to reducing agents such as diisobutylaluminum hydride and lithium triethoxyaluminum hydride. Furthermore, attempts at hydrolysis of the ester and decarboxylation under a variety of conditions only led to recovered starting material or to phenol **27**, which was presumably formed as a result of enolization between C9 and C11, followed by elimination of the nitrile and subsequent aromatization.

Since, in addition to the lack of desired reactivity, ester **26** clearly did not possess the features most suitable for the development of the complex ring-C functionality of bruceantin, we decided to modify the acetylene activation–cyclization strategy in a way that would satisfy two conditions: (1) The Michael addition should be accomplished without the introduction of an unwanted extra carbon. (2) An acetylene activating group should be used that could subsequently be modified and (or) manipulated to furnish the desired ring-C functionality. As a result, we chose to use an acetylenic sulfoxide, rather than a carbomethoxy acetylene, as the Michael acceptor. Implementation of this strategy again began with the conversion of **24** into the dianion, this time using *n*-butyllithium in THF at −78°C, followed by addition of isopropyl *p*-toluenesulfinate (17) at −78°C to give adduct **28** as an amorphous solid (81%, λ_{max} = 369 nm) (Scheme 4). Upon heating of **28** in methanol with 10 equivalents of sodium thiophenolate (18), diosphenol **29** and enone **30** were obtained in 25 and 50% yield respectively. Compound **29** was the product expected from a [2,3]-sigmatropic rearrangement followed by a base-catalyzed double bond migration, but the formation of **30** was unexpected and could only be rationalized by a reductive elimination process (eq. [2]). This type of reductive desulfurization was demonstrated recently by Theobald and Okamura (19). These results clearly indicated that the α,β-unsaturated ketone is not compatible as such with the [2,3]-sigmatropic rearrangement. However, this situation can be remedied by reducing the C11 ketone first.

After considerable experimentation, reduction was effected by treatment of **28** with lithium borohydride in THF/methanol (20) to give alcohol **31** as a 3:2 mixture of sulfoxide diastereoisomers in 77% yield. Separation of the isomers was achieved by careful silica gel chromatography to give **31 major** and **31 minor**; their stereochemistry was not determined. Compounds **31 major** and **31 minor** were then each treated with 10 equivalents of triethyl phosphite (18) in ethanol at 40°C for 5 days but only **31 major** rearranged to give diol **32** (75%). The minor isomer, even after a prolonged reaction time, gave only recovered starting material.

However, when **31 minor** was heated at 80°C for 48 h under identical conditions, a new compound assigned to be imino ether **33** was obtained in 75% yield. This initially caused some concern but it was found that **33** was also obtained as the sole product when **31 major** was heated at 80°C in the presence of 10 equivalents of triethyl phosphite, or when diol **32** was simply heated in ethanol at 80°C. This clearly demonstrated that the rearrangement of the two sulfoxide diastereomers was proceeding to give the same stereochemistry at C12, but at very different reaction rates. This must mean that one transition state involves more steric interactions than the other. Examination of molecular models showed that this can only be explained if the rearrangement proceeds from the α-face to deliver an

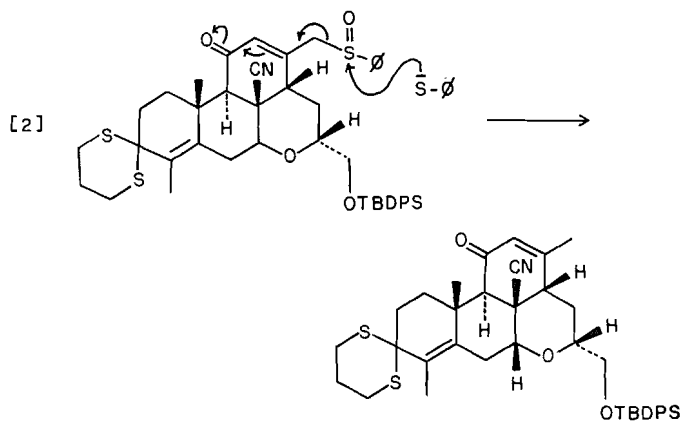
[3]It was observed that the 1,3-propane diol was insoluble in benzene and formed globules on reflux.



SCHEME 4

axial alcohol at C12 (Fig. 2). To reinforce this stereochemical assignment, a 10% nOe enhancement was observed at one of the vinyl protons when the C12 proton of **32** was irradiated.

The α (axial) assignment to the C12-OH group is also in agreement with a study reported by Hoffmann *et al.* (21). Using a simple cyclohexene whose conformation was anchored by a 4-*tert*-butyl group and whose position of the arylsulfoxy group relative to the cyclohexene was the same as in sulfoxide **31**, these authors concluded that there is a 6.2-fold preference for the formation of the axial (versus the equatorial) C—O bond



and that there is a 3.1-fold preference for an *exo* (aryl group away from the molecule) versus an *endo* (aryl group towards the molecule) transition state in that particular case. Thus, there is clearly a "six-membered ring bias" towards a quasi-axial attack of the cyclohexene via a quasi-chair conformation. However, in contrast to Hoffmann *et al.*, we have not detected a trace of the C12-β isomer on rearrangement of **31**, in spite of the fact that the sulfoxide of **31** may be involved in a 1,3-*cis* diaxial interaction with the C14—C15 bond when attacking from the α-side (see Fig. 2). Further experiments are required to establish whether the greater stereoselectivity in the case of **31** arises from a reduced conformational flexibility of the cyclohexene in **31** or whether the axial C11 hydroxyl group in **31** exerts a stereoelectronic effect favouring an antiperiplanar addition.

In conclusion, an efficient 19-step synthesis of a pentacyclic intermediate has been achieved in a 3.5% overall yield from 2-methylcyclohexane-1,3-dione and ethyl vinyl ketone. This intermediate, **33**, contains four of the five rings and seven of the 10 chiral centers of bruceantin. Its further synthetic manipulation and the general utility of the sequence **24** → **28** → **32** are currently under investigation.

Experimental section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer IR spectrophotometer model 717B using sodium chloride cells

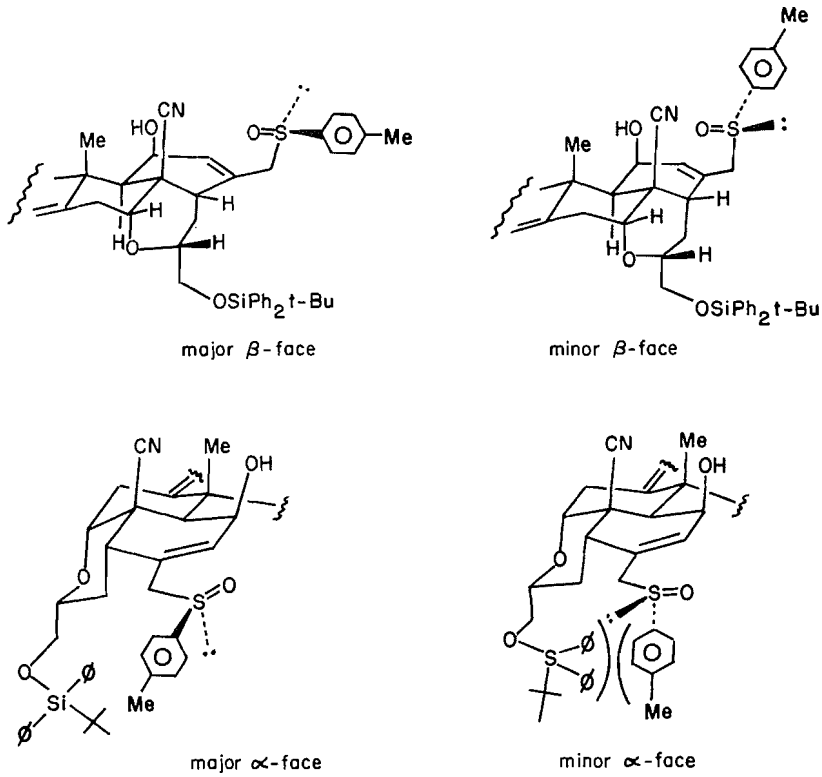


FIG. 2

(0.5 mm) and are reported in wave numbers (cm^{-1}) with polystyrene as standard. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 (200 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as standard. High resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta. Ultraviolet (UV) spectra were recorded on a Beckman spectrophotometer model 25, using quartz cells (4.5 mL).

All reactions, unless otherwise specified, were run under an inert atmosphere of Ar or N_2, and reactions requiring anhydrous conditions were performed in a flame-dried or oven-dried (120°C) apparatus. Temperatures above or below room temperature refer to bath temperatures. All solvents used in the reaction flask were anhydrous, unless otherwise stated, and were dried according to established procedures by distillation under N_2 from an appropriate drying agent (22).

Analytical TLC was performed on E. Merck precoated silica gel plates (0.25 mm). Column chromatography was performed by the method of Still *et al.* (23) with E. Merck silica gel 60 (230–400 mesh).

Preparation of enone ***14***

A solution of 3.6 g (0.017 mol) of mercuric oxide, 120 mL of 0.5% H_2SO_4, and 200 mL of THF was heated to 40°C and 4.0 g (0.0082 mol) of **8** in 20 mL of THF was added. The reaction mixture was stirred at this temperature for 4 h, cooled, and filtered through Florisil. The filtrate was saturated with NaCl and extracted with ethyl acetate. The organic extract was washed with 10% $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. After filtration and evaporation of solvent under reduced pressure, the solid was chromatographed on silica gel (hexane/ethyl acetate 4:1 as eluant) to give 3.26 g (100%) of enone **14**. An analytical sample of **14** (mp 158–159.5°C) was obtained by recrystallization from ether. IR ($CHCl_3$): 2950 (m), 2190 (w), 1720 (s), 1670 (s), 1610 (m), 1360 (m), 1320 (m); UV (95% ethanol): 243 nm (ε = 12 610); NMR (200 MHz, $CDCl_3$): 5.98–5.74 (m, 1H), 5.26–5.10 (m, 2H), 3.25 (s, 1H), 2.98–2.84 (m, 1H), 2.74–2.46 (m, 5H), 2.39 (s, 3H), 2.36–1.94 (m, 4H), 1.86 (s, 3H), 1.85–1.61 (m, 2H), 1.56 (s, 3H), 0.16 (s, 9H); HRMS (EI) *m/e* (relative intensity): 395.2277 (6.86).

Preparation of enol ether ***15***

A solution of 7.72 g (19.4 mmol) of **14** and 100 mL of dry benzene was treated with 6.47 mL (38.9 mmol) of triethylorthoformate and 0.7 g (4.07 mmol) of *p*-toluenesulfonic acid and stirred for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ and the layers were separated. The organic portion was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated *in vacuo*. The yellow solid was purified by silica gel chromatography (hexane/ethyl acetate 6:1 as eluant) to yield 7.36 g (89%) of **17**. An analytical sample of **17** (mp 102–105°C) was obtained by recrystallization from ether/hexane. IR ($CHCl_3$): 2910 (s), 2240 (m), 2160 (m), 1710 (s), 1650 (s), 1380 (s), 1360 (s); UV (95% ethanol): 248 nm (ε = 10 582); NMR (200 MHz, $CDCl_3$): 5.96–5.74 (m, 1H), 5.47 (t, *J* = 4 Hz, 1H), 5.26–5.08 (m, 2H), 3.86 (q, *J* = 7 Hz, 2H), 3.28 (s, 1H), 2.86–2.46 (m, 4H), 2.40 (s, 3H), 2.39–2.06 (m, 3H), 1.96–1.84 (m, 1H), 1.81 (s, 3H), 1.78–1.56 (m, 1H), 1.36 (s, 3H), 1.29 (t, *J* = 7 Hz, 3H), 0.17 (s, 9H); HRMS (EI) *m/e* (relative intensity): 423.2604 (46.73).

Preparation of bromide ***16***

To a solution of 7.21 g (17 mmol) of enol ether **15** in 1.5 L of THF and 42 mL of water was added dropwise 5.97 g (18.7 mmol) of pyridinium bromide perbromide in 50 mL of THF over 5 min. Towards the end of the addition the solution became turbid, so an additional 25 mL of water was added. At the end of the addition the reaction mixture was stirred for 5 min. After the solution was washed with 10% $NaHCO_3$, water, and brine, it was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate 3:1 as eluant) furnished 7.07 g (88%) of **16**. An analytical sample of **16** (mp 134–137°C) was prepared by recrystallization from ether/hexane. IR ($CHCl_3$): 2970 (s), 2260 (w), 2190 (m), 1720 (s), 1680 (s), 1610 (m), 1360 (s), 1320 (s); UV (95% ethanol): 257 nm (ε = 15 083); NMR (200 MHz, $CDCl_3$): 5.90–5.70 (m, 1H), 5.40 (dd, *J* = 2 Hz, *J* = 2 Hz, 1H), 5.26–5.10 (m, 2H), 3.18 (s, 1H), 2.84–2.56 (m, 5H), 2.43 (s, 3H), 2.38–2.0 (m, 3H), 1.95 (s, 3H), 1.93 (s, 3H), 0.14 (s, 9H); HRMS (EI) *m/e* (relative intensity): 473.1395 (1.16).

Preparation of dienone ***17***

To a solution of 8.87 mL (71.7 mmol) of DBN and 100 mL of dry THF was added 6.83 g (14.4 mmol) of bromide **16** in 50 mL of THF via a dropping funnel over 10 min. After complete addition, the solution was stirred for 20 min and then quenched with 50 mL of saturated NH_4Cl. The layers were separated and the organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. After evaporation of solvent *in vacuo* and purification by silica gel chromatography (hexane/ethyl acetate 3:1 as eluant), 4.45 g (78%) of dienone **17** was obtained. An analytical sample of **17** (mp 167–168°C) was obtained by recrystallization from ether/hexane. IR ($CHCl_3$): 2970 (m), 2890 (m), 2250 (m), 2190 (m), 1720 (s), 1660 (s), 1630 (m), 1590 (m), 1360 (m), 1320 (m); UV (95% ethanol): 282 nm (ϵ = 17 300); NMR (200 MHz, $CDCl_3$): 6.85 (d, J = 10 Hz, 1H), 6.04 (d, J = 10 Hz, 1H), 6.02–5.82 (m, 1H), 5.36–5.17 (m, 2H), 3.53 (s, 1H), 2.88–2.44 (m, 5H), 2.42 (s, 3H), 1.93 (s, 3H), 1.57 (s, 3H), 0.17 (s, 9H); HRMS (EI) m/e (relative intensity): 393.2123 (8.18).

Preparation of diol ***19***

A mixture of 302 mL of *tert*-butanol, 38.2 mL of water, 114 mL of THF, 3.24 g (24 mmol) of *N*-methylmorpholine-*N*-oxide, and 8.59 g (21.8 mmol) of **18** was stirred until a homogenous solution was obtained, at which time 2 mL of a 4% (w/v) water solution of OsO_4 (0.3 mmol) was added and stirring continued for 18 h. To the solution was then added 2.2 g of Florisil and 1 g of $Na_2S_2O_4$; the solution was stirred for 5 min and then filtered through Celite. The solvent was evaporated under reduced pressure and the residue was taken up in ethyl acetate, washed with 5% HCl, water, and brine. After drying over anhydrous $MgSO_4$, filtration, and evaporation of solvent *in vacuo*, the solid was purified by silica gel chromatography (hexane/ethyl acetate 1:4 as eluant) to give 7.85 g (85%) of diol **19**. IR ($CHCl_3$): 3700–3300 (br, m), 2950 (s), 2250 (m), 2190 (m), 1720 (s), 1660 (s), 1630 (m), 1590 (m), 1380 (m), 1360 (s), 1330 (s); UV (95% ethanol): 278 nm (ϵ = 19 340); NMR (200 MHz, $CDCl_3$), major diastereomer: 6.81 (d, J = 10 Hz, 1H), 5.95 (d, J = 10 Hz, 1H), 4.05–3.92 (m, 1H), 3.84–3.40 (m, 3H), 3.08 (dd, J = 3 Hz, J = 12 Hz, 1H), 2.86–2.52 (m, 2H), 2.40 (s, 3H), 1.89 (s, 3H), 1.55 (s, 3H), 0.12 (s, 9H); minor diastereomer: 6.83 (d, J = 10 Hz, 1H), 5.97 (d, J = 10 Hz, 1H), 4.05–3.92 (m, 1H), 3.84–3.40 (m, 3H), 3.08 (dd, J = 3 Hz, J = 12 Hz, 1H), 2.86–2.52 (m, 2H), 2.40 (s, 3H), 1.89 (s, 3H), 1.55 (s, 3H), 0.14 (s, 9H); HRMS (EI) m/e (relative intensity): 427.2159 (1).

Preparation of enone ***20***

A solution of 300 mL of benzene, 21.4 mL (0.3 mol) of 1,3-propane diol, and 28.2 g (0.15 mol) of *p*-toluenesulfonic acid was brought to reflux for 2 h and the water was azeotropically removed via a Dean–Stark apparatus. The solution was cooled to 40°C and 2.11 g (0.005 mol) of diol **19** in 20 mL of dry benzene was added. The reaction mixture was rapidly stirred at this temperature for 4 h. The benzene was removed under reduced pressure and the residue was taken up in ethyl acetate and washed three times with saturated $NaHCO_3$, water, and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and solvent evaporated. The solid was purified by silica gel chromatography (hexane/ethyl acetate 1:4 as eluant) to give 1.44 g (90%) of alcohol **20** and 0.5 g of starting material **19**. IR ($CHCl_3$): 3620 (m), 3600–3300 (br, m), 2950 (m), 2900 (m), 2260 (w), 2190 (w), 1720 (s), 1660 (s), 1620 (m), 1360 (s), 1320 (m); UV (95% ethanol): 245 nm (ϵ = 12 610); NMR (200 MHz, $CDCl_3$): 4.21 (t, J = 3 Hz, 1H), 4.16–3.86 (m, 3H), 3.78–3.52 (m, 2H), 3.36 (s, 1H), 3.36–2.72 (m, 5H), 2.44 (s, 3H), 1.81 (s, 3H), 1.60 (s, 3H), 0.18 (s, 9H); HRMS (EI) m/e (relative intensity): 427.2166 (12.82).

Preparation of acetylene ***21***

A solution of 5.3 g (0.012 mol) of enone **20** in 100 mL of dry CH_3CN was stirred with 11.8 g (0.042 mol) of tetrabutylammonium chloride and 5.61 g (0.097 mol) of potassium fluoride at room temperature for 0.5 h. The acetonitrile was evaporated under reduced pressure and the residue taken up in ethyl acetate and washed with saturated NH_4Cl, water, and brine. After drying over anhydrous $MgSO_4$ and filtering, the solvent was evaporated *in vacuo*. The solid obtained was purified by silica gel chromatography (hexane/ethyl acetate 1:2 as eluant) to give 4.4 g (100%) of acetylene **21**. IR ($CHCl_3$): 3320 (m), 2950 (m), 2880 (m), 2260 (w), 1720 (m), 1670 (s), 1625 (m), 1360 (m); UV (95% ethanol): 247 nm (ϵ = 12 739); NMR (200 MHz, $CDCl_3$): 3.93 (t, J = 4 Hz, 1H), 3.80–3.48 (m, 3H), 3.28–2.74 (m, 4H), 2.93 (s, 1H), 2.39 (d, J = 2.7 Hz, 1H), 1.18 (s, 3H), 1.59 (s, 3H); HRMS (EI) m/e (relative intensity): 355.1787 (96.25).

Preparation of silyl ethers ***22*** *and* ***23***

A solution of 4.40 g (0.012 mol) of acetylene **21** in 200 mL of dry DMF was stirred with 6.46 mL (0.025 mol) of *tert*-butyldiphenylsilyl chloride and 3.98 g (0.049 mol) of imidazole for 10 h at room temperature. The reaction mixture was poured into saturated NH_4Cl and diluted with 100 mL of benzene. The layers were separated and the organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and solvent evaporated under reduced pressure. Silica gel chromatography (hexane/ethyl acetate 7:3 as eluant) gave 5.31 g of **22** and 0.9 g of **23** (85% combined yield). An analytical sample of **22** (mp 199–200°C) and **23** (mp 207–208.5°C) was obtained by recrystallization from hexane/ethyl acetate. Major diastereomer **22**: IR ($CHCl_3$): 3310 (s), 2930 (s), 2860 (s), 2250 (w), 1720 (s), 1660 (s), 1620 (m), 1360 (s); UV (95% ethanol): 247 nm (ϵ = 13 260); NMR (200 MHz, $CDCl_3$): 7.74–7.34 (m, 10H), 3.88 (t, J = 3 Hz, 1H), 3.80–3.74 (m, 3H), 3.31 (s, 1H), 3.24–3.00 (m, 2H), 2.90–2.74 (m, 1H), 2.42 (s, 3H), 2.40 (d, J = 2 Hz, 1H), 1.84 (s, 3H), 1.61 (s, 3H), 1.03 (s, 9H); HRMS (EI) m/e (relative intensity): 536.2254 (M − C_4H_9, 100); minor diastereomer **23**: IR ($CHCl_3$): 3320 (m), 2940 (m), 2870 (m), 2260 (w), 1720 (m), 1670 (s), 1620 (s), 1360 (m); UV (95% ethanol): 247 nm (ϵ = 13 460); NMR (200 MHz, $CDCl_3$): 7.76–7.38 (m, 10H), 4.02 (t, J = 3 Hz, 1H), 4.01 (m, 1H), 3.92–3.80 (m, 2H), 3.31 (s, 1H), 3.31–3.20 (m, 1H), 2.96–2.60 (m, 2H), 2.44 (s, 3H), 2.35 (d, J = 2 Hz, 1H), 2.16–1.92 (m, 3H), 1.79 (s, 3H), 1.56 (s, 3H), 1.10 (s, 9H); HRMS (EI) m/e (relative intensity): 536.2267 (M − C_4H_9, 87.98).

Preparation of dithianes ***24*** *and* ***25***

A solution of 1.28 g (2.16 mmol) of ether **22** in 3 mL each of dry THF and Et_2O was treated with 4.0 mL (32.5 mmol) of $BF_3 \cdot OEt_2$ and 0.48 mL (4.77 mmol) of 1,3-propane dithiol at room temperature for 3 h. The reaction mixture was *carefully* poured into cold saturated $NaHCO_3$ and diluted with 50 mL of ethyl acetate. Separation of the layers and washing of the organic phase with water and brine, followed by drying over anhydrous $MgSO_4$, filtration, and evaporation of solvent under reduced pressure, gave a yellow solid. Purification by silica gel chromatography (hexane/ethyl acetate 3:1 as eluant) gave 1.42 g (96%) of dithiane **24**. An analytical sample of **24** (mp 180–183°C) was obtained by recrystallization from hexane/ether. IR ($CHCl_3$): 3310 (s), 2930 (s), 2860 (s), 2250 (w), 1720 (s), 1590 (w), 1420 (m), 1360 (s); NMR (200 MHz, $CDCl_3$): 7.76–7.36 (m, 10H), 3.80–3.44 (m, 3H), 3.75 (t, J = 3 Hz, 1H), 3.18–2.46 (m, 9H), 3.09 (s, 1H), 2.42 (s, 3H), 2.35 (d, J = 2 Hz, 1H), 2.28–1.72 (m, 7H), 2.00 (s, 3H), 1.48 (s, 3H), 1.08 (s, 9H); HRMS (EI) m/e (relative intensity): 683.2920 (39.45).

The same procedure was followed for the preparation of dithiane **25** (84%). An analytical sample of **25** (mp 196–198°C) was obtained by recrystallization from ether/hexane. IR ($CHCl_3$): 3320 (s), 2940 (s), 2860 (s), 2260 (m), 1710 (s), 1600 (m), 1420 (s), 1390 (m), 1360 (s), 1280 (s); NMR (200 MHz, $CDCl_3$): 7.78–7.38 (m, 10H), 4.12–3.99 (m, 1H), 3.89 (t, J = 3 Hz, 1H), 3.88–3.76 (m, 2H), 3.24–2.98 (m, 3H), 3.15 (s, 1H), 2.80–2.46 (m, 5H), 2.42 (s, 3H), 2.40–1.78 (m, 8H), 1.96 (s, 3H), 1.42 (s, 3H), 1.08 (s, 9H); HRMS (EI) m/e (relative intensity): 683.2906 (6.38).

Preparation of keto ester ***26***

A solution of 0.2 mL (0.98 mmol) of hexamethyldisilazine and 10 mL of dry THF was cooled to −30°C and 0.61 mL (0.98 mmol) of 1.6 M *n*BuLi in hexane was added dropwise via a syringe. The mixture was stirred for 15 min and then treated with acetylene **24** in 5 mL of dry

THF. After 2 h of stirring the temperature was lowered to −78°C and 0.018 mL (0.21 mmol) of dimethyl carbonate was added. The reaction mixture was maintained at this temperature for 4 h and then poured into saturated ammonium chloride. The layers were separated and the organic portion was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and solvent evaporated *in vacuo*. Purification by silica gel chromatography (hexane/ethyl acetate 3:1 as eluant) gave 92 mg (84%) of keto ester **26**. An analytical sample of **26** (mp 176–178°C) was obtained by recrystallization from ether/hexane. IR ($CHCl_3$): 2820 (s), 2850 (s), 2240 (w), 1740 (s), 1680 (s), 1640 (m), 1600 (w), 1430 (s), 1380 (m), 1360 (m), 1340 (m); UV (95% ethanol + 5% NaOH): 390 nm (ϵ = 60 975); NMR (200 MHz, $CDCl_3$): 7.78–7.36 (m, 10H), 6.00 (s, 1H), 3.87 (t, J = 3 Hz, 1H), 3.84–3.52 (m, 3H), 3.73 (s, 3H), 3.34–2.40 (m, 11H), 2.0 (s, 3H), 1.45 (s, 3H), 1.04 (s, 9H).

Preparation of keto sulfoxide 28

A solution of 500 mg (0.73 mmol) of acetylene **24** and 60 mL of dry THF was cooled to −78°C. To this via a syringe was added 0.88 mL (2.2 mmol) of 2.5 M *n*BuLi in hexane, and after 15 min 261 mg (1.32 mmol) of isopropoxy-*p*-toluenesulfinate in 1 mL of THF was added. The reaction mixture was warmed to room temperature gradually and stirred for 5 h. The solution was poured into saturated NH_4Cl and the layers were separated. The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and solvent evaporated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate 1:1 as eluant) gave 490 mg (81%) of keto sulfoxide **28**. IR ($CHCl_3$): 2940 (s), 2860 (s), 2240 (w), 1685 (s), 1640 (m), 1605 (m), 1500 (m), 1470 (m), 1440 (m), 1385 (m), 1370 (m), 1350 (m), 1310 (m); UV (95% ethanol + 5% NaOH): 369 nm (ϵ = 30 400); NMR (200 MHz, $CDCl_3$): 7.78–7.32 (m, 14H), 5.61, 5.56 (C13-H from each sulfoxide diastereomer), 3.96–2.48 (m, 16H), 2.44 (s, 3H), 2.00 (s, 3H), 1.46 (s, 3H), 1.06 (s, 9H).

Preparation of diosphenol 29 and enone 30

A solution of 31 mg (0.037 mmol) of keto sulfoxide **28** and 5 mL of anhydrous methanol was treated with 0.62 mL (0.17 mmol) of 0.11 M sodium thiophenolate and refluxed for 60 h. After cooling, the methanol was evaporated under reduced pressure. The residue was taken up in 10 mL of ethyl acetate and washed with saturated NH_4Cl, water, and brine. Following drying over anhydrous $MgSO_4$ and filtration, the solvent was evaporated *in vacuo*. Purification by silica gel chromatography (hexane/ethyl acetate 85:15 as eluant) gave 7 mg of diosphenol **29** and 14 mg of enone **30** (79% combined yield). Diosphenol **29**: IR ($CHCl_3$): 3600–3300 (br, w), 2930 (s), 2860 (s), 2250 (w), 1720 (w), 1675 (s), 1645 (m), 1595 (w), 1420 (m), 1380 (m), 1360 (m), 1340 (m), 1300 (m); UV (95% ethanol): 276 nm; (95% ethanol + 5% NaOH): 324 nm; NMR (200 MHz, $CDCl_3$): 7.72–7.34 (m, 10H), 3.82 (t, J = 3 Hz, 1H), 3.79–3.42 (m, 3H), 3.20–2.82 (m, 3H), 2.76–2.42 (m, 8H), 1.99 (s, 3H), 1.96 (s, 3H), 1.45 (s, 3H), 1.04 (s, 9H).

Enone **30**: IR ($CHCl_3$): 2930 (s), 2240 (w), 1680 (s), 1640 (m), 1600 (m), 1470 (m), 1450 (m), 1430 (m), 1380 (m); UV (95% ethanol): 256 nm; NMR: 7.74–7.36 (m, 10H), 5.89 (s, 1H), 3.96–3.50 (m, 4H), 3.20–2.84 (m, 2H), 2.78–2.38 (m, 5H), 2.26–1.58 (m, 9H), 1.98 (s, 3H), 1.46 (s, 3H), 1.04 (s, 9H).

Preparation of hydroxy sulfoxides 31 major and 31 minor

A solution of 25 mL of dry THF, 2.5 mL of anhydrous methanol, and 26 mg (1.19 mmol) of lithium borohydride was stirred at room temperature for 20 min. Then 100 mg (0.12 mmol) of keto sulfoxide **28** in 1 mL of THF was added and stirring was continued for 10 min. The reaction mixture was diluted with 20 mL of reagent grade ether and 1 mL of 10% HCl. The mixture was then washed with 10% HCl, water, and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and solvent evaporated under reduced pressure. Silica gel chromatography (hexane/ethyl acetate 1:1 as eluant) furnished 46 mg of **31 major** and 31 mg of **31 minor** (77% combined yield). **31 major**: IR ($CHCl_3$): 3580 (w), 3500–3200 (br m), 2930 (s), 2850 (s), 2240 (w), 1600 (w), 1470 (m), 1420 (m), 1365 (m); NMR (200 MHz, $CDCl_3$): 7.78–7.32 (m, 14H), 5.44 (d, J = 4 Hz, 1H), 4.35 (dd, J = 3 Hz, J = 4 Hz, 1H), 3.87 (t, J = 2 Hz, 1H), 3.80–3.24 (m, 5H), 3.22–2.50 (m, 8H), 2.44 (s, 3H), 1.98 (s, 3H), 1.66 (s, 3H), 1.05 (s, 9H).

31 minor: IR ($CHCl_3$): 3580 (w), 3540–3300 (br, w), 2930 (s), 2850 (s), 2230 (w), 1600 (w), 1500 (m), 1470 (m), 1430 (s), 1390 (m); NMR (200 MHz, $CDCl_3$): 7.74–7.32 (m, 14H), 5.44 (d, J = 4.5 Hz, 1H), 4.32 (dd, J = 3 Hz, J = 4.5 Hz, 1H), 3.88 (t, J = 3 Hz, 1H), 3.76–3.60 (m, 4H), 3.28–2.48 (m, 8H), 2.44 (s, 3H), 2.30–1.72 (m, 7H), 1.96 (s, 3H), 1.66 (s, 3H), 1.04 (s, 9H).

Preparation of diol 32

A solution of 19 mg (0.023 mmol) of **31 major** and 5 mL of anhydrous ethanol was heated at 40°C for 5 days with 0.039 mL (0.23 mmol) of triethyl phosphite. After cooling and evaporation of solvent the residue was purified by silica gel chromatography (hexane/ethyl acetate 1:1 as eluant) to give 12 mg (75%) of diol **32**. IR ($CHCl_3$): 3610 (m), 3550–3250 (br, w), 2920 (s), 2850 (s), 2240 (w), 1590 (w), 1420 (m), 1380 (m), 1360 (m); NMR (200 MHz, $CDCl_3$): 7.78–7.34 (m, 10H), 5.34 (s, 1H), 5.28 (s, 1H), 4.32 (dd, J = 3.5 Hz, J = 8 Hz, 1H), 4.21 (d, J = 3.5 Hz, 1H), 3.80 (t, J = 2 Hz, 1H), 3.76–3.40 (m, 3H), 3.22–2.02 (m, 12H), 1.98 (s, 3H), 2.58 (s, 3H), 1.05 (s, 9H).

Preparation of imino ether 33

A solution of 14 mg (0.017 mol) of **31 minor** and 5 mL of anhydrous ethanol was heated at 80°C for 48 h in the presence of 0.029 mL (0.17 mmol) of triethyl phosphite. After cooling, and evaporation of solvent *in vacuo*, the residue was purified by silica gel chromatography (hexane/ethyl acetate 1:1 as eluant) to deliver 9 mg (75%) of imino ether **33**.

The other sulfoxide diastereoisomer **31 major** can be subjected to the same conditions to give **33** (76%). IR ($CHCl_3$): 3280 (w), 2820 (s), 2850 (s), 1695 (s), 1600 (w), 1470 (m), 1430 (m), 1380 (m), 1360 (m); NMR (200 MHz, $CDCl_3$): 7.78–7.56 (m, 10H), 5.24 (s, 1H), 5.19 (s, 1H), 4.50 (d, J = 5 Hz, 1H), 4.41 (d, J = 5 Hz, 1H), 4.00 (t, J = 3 Hz, 1H), 3.80–3.46 (m, 3H), 3.18–2.94 (m, 2H), 2.80–2.00 (m, 11H), 1.93 (s, 3H), 1.90–1.55 (m, 3H), 1.07 (s, 3H), 1.04 (s, 9H).

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