Synthesis of the Antileukemic Agent (±)-Steganone Using a Stereoconvergent Biaryl Coupling Reaction

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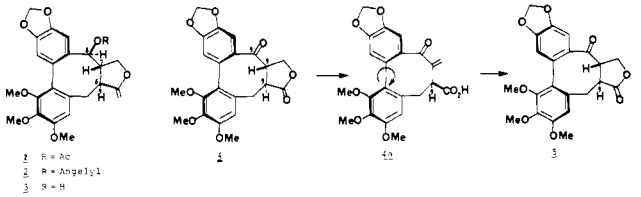
Received February 12, 1985

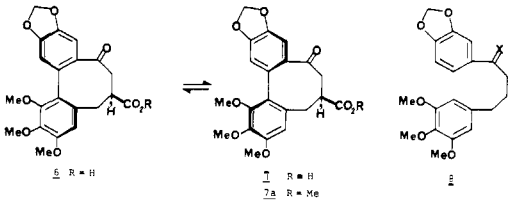
Abstract: The total synthesis of (±)-steganone (**4**) has been achieved in a stereoselective manner from piperonal. The cinnamate derivative **15** was oxidized by using $Tl(OCOCF_3)_3$ in TFA to give the biaryl **26** (81%). Reduction of **26** with $LiAlH_4$ gave **27**, which was converted into the cyclopropylcarbinol **10** by the Simmons–Smith reaction. The same key substrate was also available by $Tl(OCOCF_3)_3$ oxidation of the cyclopropane adduct **9** (X = OMe) followed by reduction with $LiAlH_4$ to give **10**. The former sequence is the preferred one. Solvolysis of **10** in AcOH accomplished ring expansion and the regio- and stereospecific introduction of the C-8 oxygen substituent to give **34**. Hydroboration of **34** followed by base hydrolysis gave the diol **35**, which establishes the correct relative stereochemistry between C-8 and the biaryl twist. Jones oxidation of **35** gave the known oxoacid **7**, which was converted into (±)-steganone (**4**) by using the literature procedure.

In 1972, Kupchan[1] reported the isolation from *Steganotaenia araliacea* Hochst four dibenzocyclooctadiene lignans that exhibited significant activity in vivo against the P-388 leukemia in mice and in vitro against cells derived from human carcinoma of the nasopharynx (KB). These compounds, steganacin (**1**), steganangin (**2**), steganol (**3**), and steganone (**4**), belong to the unusual dibenzocyclooctadiene lignans[2] and, as such, immediately presented a very effective challenge for synthesis. This has been met by



reports of several syntheses that can be divided into three main classes. The first, and most efficient synthesis, by Raphael[3] involves the construction of a 9-pyrrolidinophenanthrene by conrotatory cyclization of a stilbene derivative, followed by a two-carbon ring expansion. An important feature of this synthesis is that it allows for the direct regiospecific introduction of the benzylic oxygen functionality at C-8. The second very effective strategy was developed by Ziegler[4] that involves the examination of modifications of the Ullmann reaction to give unsymmetrically substituted biaryls. The third, from a biosynthetic point of view, most interesting strategy has been reported by Kende[5] and uses the so-called non-phenolic oxidation methodology,[6] which resulted in the direct formation of the crucial biaryl bond concomitant with the eight-membered ring. Unfortunately, the attractiveness of the non-phenolic oxidation approach is curtailed by the apparent inability to carry out oxidative coupling in the presence of a benzylic oxygen substituent. Consequently, while this approach is direct, the C-8 oxygen substituent has to be introduced at a later stage by benzylic oxidation.[7]

An intriguing stereochemical problem occurred during the synthesis of steganone (**4**) and was first described in detail by Raphael.[3] All the syntheses proceed through the oxoacid **6**, which has the opposite biaryl twist relative to the ester group, required for the synthesis of steganone (**4**). Fortunately, the oxoacid **6**



was equilibrated with its biaryl twist rotamer by heating in xylene (135 °C) to give a 1:1 mixture of **6** and **7**. When the "wrong" oxoacid **6** is treated with aqueous KOH/CH_2O, followed by Jones oxidation (CH_2O treatment results in reduction), isosteganone (**5**) was formed (78%), which was thermally isomerized to steganone (**4**) through β elimination to **4a** and recyclization to **4**. It should be noted that epimerization at the carboxyl (or ester) group at C-6 is equivalent to a reversal of the biaryl twist. All the syntheses arrive at isosteganone (**5**) and thermally isomerize it into steganone **4**. Fortunately, this transformation is almost quantitative because the driving force is provided by the movement of the C-8 carbonyl group in **5** (ν_{max} = 1710 cm^{-1}) into planarity with the piperonyl ring to give steganone **4** (ν_{max} = 1665 cm^{-1}).

Given the background outlined above, there are two problems that present themselves. First, how can non-phenolic biaryl coupling be carried out in the presence of a benzylic substituent, and second, is this strategy compatible with the direct formation of the requisite biaryl with the correct relative configuration with respect to the configuration at C-6?

Results

All our attempts to conduct non-phenolic oxidation using a range of reagents, VOF_3,[6] $FeCl_3$,[8] and $Tl(OCOCF_3)_3$,[9] on the

(1) Kupchan, S. M; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. J.; Bryan, R. F., *J. Am. Chem. Soc.* **1973**, *95*, 1335.

(2) For a recent general review on the synthesis of lignans and neolignans, see: Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, No, 2, 75.

(3) Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674. Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Chem. Commun.* **1974**, 430. Hughes, L. R.; Raphael, R. A. *Tetrahedron Lett.* **1976**, 1543.

(4) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790. Ziegler, F. E.; Fowler, K. W.; Kanfer, S. J. *Ibid.* **1976**, *98*, 8282. Ziegler, F. E.; Fowler, K. W.; Sinha, N. D. *Tetrahedron Lett.* **1978**, 2767.

(5) Kende, A. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 267. Kende, A. S.; Liebeskind, L. S.; Kubiak, C.; Eisenberg, R. *Ibid.* **1976**, *98*, 6389.

(6) Kupchan, S. M.; Liepa, A. J. Kameswaran, V.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 6861. Kupchan, S. M.; Kamwswaran, V.; Lynn, J. T.; Williams, D. K.; Liepa, A. J. *Ibid.* **1975**, *97*, 5622. Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K.; Kameswaran, V. *J. Org. Chem.* **1976**, *41*, 4047. Kupchan, S. M.; Khingra, O. P.; Kim, C.-K. *Ibid.* **1976**, *41*, 4049.

(7) The Kende synthesis of (±)-steganone reports extensive efforts to introduce the required benzylic oxygen atom at C-8 prior to oxidation to the biaryl system and states that attempted non-phenolic oxidation of substrates similar to **8** failed.

(8) Ferric chloride supported on silica gel is a mild procedure for the oxidative coupling of phenols and phenol ethers: Jempty, T. C.; Millar, J. L.; Mazur, Y. *J. Org. Chem.* **1980**, *45*, 749.

(9) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338; McKillop, A.; Fowler, J. S.; Zelesko, M. J.; Hunt, J. D.; Taulor, E. C.; McGillivray, G. *Tetrahedron Lett.* **1969**, 2423, 2427. For the oxidative dimerization of cinnamic acids using $Tl(OCOCF_3)_3$ see: Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A. *Tetrahedron Lett.* **1978**, 3623. And: *J. Org. Chem.* **1981**, *46*, 3078. McKillop, A.; Turrell, A. G.; Taylor, E. C. *J. Org. Chem.* **1977**, **42**, 764. This reference describes the oxidation of 1,3-bis(3,4-dimethoxyphenyl)propane to a biphenyl, bridged by three carbon atoms.

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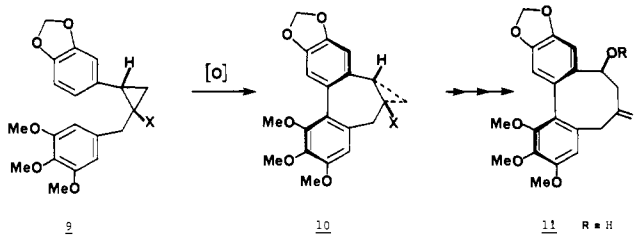
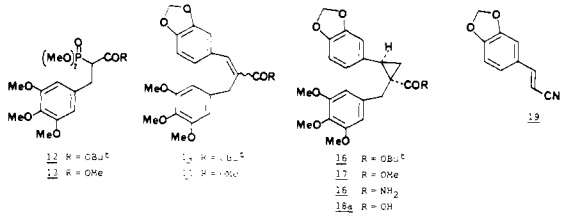
Scheme I



substrates **8** (X = H, OH; H, OAc; H, CN; H, SO_2Ph; OCH_2-CH_2O; OCH_2CH_2S; $OCH_2CH_2SO_2$; and H, $SiMe_3$) uniformly resulted in extensive decomposition with no clear evidence for the formation of the biaryl-coupled products. Consequently, a less direct approach was required that at least would enable the regiospecific introduction of an oxygen substituent at C-8. A plausible way to achieve this initial objective is to disguise both the eventual eight-membered ring and the oxygen functionality at C-8 in the form of a cyclopropane derivative. Controlled opening of the cyclopropane ring at an appropriate stage has the inherent potential to result in ring expansion and concomitant regio- and stereoselective placement of the C-8 oxygen atom. this strategy is outlined in Scheme I. The scheme requires the regiospecific synthesis of **9** (X = CO_2R), its oxidation to the biaryl **10** (X = CO_2R), and finally ring expansion, most probably via a cyclopropylcarbinol solvolysis reaction[10] on **10** (X = CH_2OH) to give the dibenzocyclooctadiene **11**.

3,4,5-Trimethoxybenzyl bromide was treated with *t*-$BuO_2CCH_2P(O)(OEt)_2$/NaH/THF to give the phosphonate **12**, which was directly treated with NaH/piperonal to provide the α,β-unsaturated ester **14** as a mixture of *E* and *Z* isomers (2:1) in 38% yield. It was not necessary to separate these isomers, since

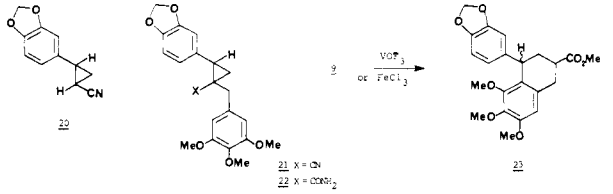


the treatment of α,β-unsaturated carbonyl compounds with dimethylsulfoxonium methylide is known to be nonstereospecific.[11] In the event, when **14** was treated with $Me_2S^+(O)CH_3I^-$/NaH/THF, a single cyclopropane stereoisomer **16** was formed in 81.6% yield. Part of the chemical proof for the stereochemistry depicted for **16** was obtained in the following chemical correlations. (The choice, at this stage, of a *tert*-butyl ester was dictated by its ready removal under acidic conditions.)

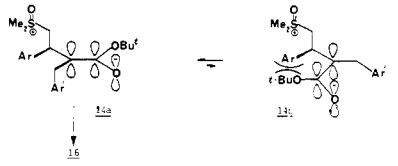
The α,β-unsaturated nitrile **19** was converted into the cyclopropylnitrile **20**, using $Me_2S^+(O)CH_3I^-$/NaH/THF, and alkylated with 3,4,5-trimethoxybenzyl bromide/LiN-i-Pr_2/THF/−78 °C to give a single stereochemically homogeneous adduct **21**. The alkylation of **20** has taken place with complete inversion,[12] and its assignment of stereochemistry ultimately rests upon the oxidative cyclization reactions described below. Treatment of **21** with alkaline hydrogen peroxide gave the amide **22**, which was different (TLC, NMR, mp) from the amide **18** prepared by treating **16** with TFA to give the corresponding acid **18a** and standard conversion ($SOCl_2$, followed by NH_3) into **18**. Having established that the two routes to substrates suitable for biaryl oxidative cyclization give opposite stereochemistry about the cyclopropane, the only question is which is the correct cis arrangement of piperonyl to 3,4,5-trimethoxybenzyl? Obviously, only one of the cyclopropane stereoisomers is capable of undergoing oxidative coupling to a biaryl, thereby establishing the relative stereochemistry in a chemically conclusive fashion.

The *tert*-butyl ester **16** proved to be too labile to the acidic conditions normally used in non-phenolic oxidative cyclizations; consequently, we used the corresponding methyl ester **17**. Treatment of the *tert*-butyl ester **16** with *p*-TsOH·H_2O/toluene/reflux gave the corresponding carboxylic acid **16** (R = OH), which was exposed to diazomethane to provide the methyl ester **17** (92%). It should be noted that attempted cyclopropanation of **15** (see later) with $Me_2S^+(O)CH_3I^-$/NaH/THF resulted in 1,2-addition, whereas, the *tert*-butyl ester **14** gave the 1,4-adduct **16**.

Treatment of the ester **17** with $Tl(OCOCF_3)_3$/TFA/0 °C gave the biaryl **10** (X = CO_2Me) in 43% yield, as a single stereochemically homogeneous compound, assigned the relative configuration shown, based upon an alternative synthesis of the reduction product **10** (X = CH_2OH). The use of other one-electron oxidants such as VOF_3 or $FeCl_3$, silica gel, did not give any oxidative coupling but caused a Lewis acid-promoted intramolecular alkylation to give **23**.[13] The formation of the required



coupled product **10** (X = CO_2Me) allows the unambiguous assignment of the relative configurations of the various substituted cyclopropanes **16**, **17**, **18**, **21**, and **22** as shown. The benzylation of **20** must have taken place with complete inversion of configuration. The stereoconvergent cyclopropanation of the α,β-unsaturated ester **14** presumably implies that the intermediate sulfoxonium ion **14a** is more stable than the conformer **14b** where



there is a severe nonbonded interaction between the *t*-BuO^- group and the piperonyl ring. (A similar picture for **20**, except that the cyclopropane ring is already formed, would predict inversion to give **21**.)

The $Tl(OCOCF_3)_3$ biaryl coupling reaction was carried out in neat TFA for the following rationale: Treatment of **17** with $Tl(OCOCF_3)_3/CH_2Cl_2$/TFA(190 equiv) gave **10** (X = CO_2Me) in only 5% yield; the major product was the arylthallium adduct **24** (90%).[14] When the arylthallium bis(trifluoroacetate) derivative **24** was worked up with KI/I_2, the aryliodide **25** was isolated in 76% yield.[14] Photolysis of **25** in acetonitrile resulted in the slow

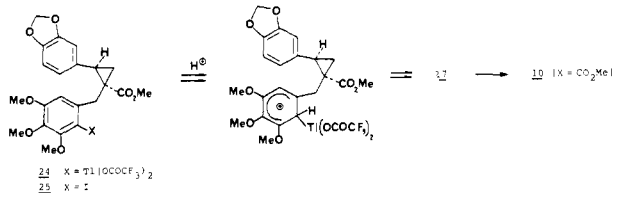
(10) Cyclopropylcarbinyl cation rearrangements, see: Olah, G. A.; Liang, G. *J. Am. Chem. Soc.* **1976**, *98*, 7026. Friedrich, E. C.; Jassawalla, J. D. C. *J. Org. Chem.* **1979**, *44*, 4224. For a comprehensive review describing cyclopropane ring opening, see: Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 577. Hanack, M.; Schneider, H.-J. *Ibid.* **1967**, *6*, 666. Solvolytic rearrangement route to ring-expanded steroids: Steinberg, N. G.; Rasmusson, G. H.; Reamer, R. A. *J. Org. Chem.* **1979**, *44*, 2294. Marshall, J. A.; Ellison, R. H. *Ibid.* **1975**, *40*, 2070. Hudrlik, P. F.; Rudnick, L. R.; Korzeniowski, S. H. *J. Am. Chem. Soc.* **1973**, *95*, 6848. Whalen, D. L.; Cooper, J. D. *J. Org. Chem.* **1978**, *43*, 432. For a general review of cyclopropane chemistry: see: Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809. Other examples of cyclopropanes in ring expansion reactions: Kohout, L.; Fajkos, J. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1613. Bellamy, A. J.; Whitman, G. H. *Tetrahedron* **1968**, *24*, 247. Caine, D.; Gupton, J. T. *J. Org. Chem.* **1974**, *39*, 2654. Seebach, D.; Braun, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 49. Reese, C. B.; Shaw, A. *J. Am. Chem. Soc.* **1970**, *92*, 2566. Parham, W. E.; Schweizer, E. E. *Org. React.*, **1963**, *13*, 55. Amice, P.; Blanco, L.; Conia, J. M. *Synthesis* **1976**, 196.

(11) For a description of the stereochemical consequences of dimethylsulfoxonium methylide additions to conjugated esters, see: Trost, B. M.; Melvin, L. S., Jr. "Sulfur Ylides, Emerging Synthetic Intermediates"; Academic Press: New York, 1975; pp 77–107.

(12) Walborsky, H. M.; Motes, J. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445. Fox, M. A.; Chem, C.-C.; Campbell, K. A. *J. Org. Chem.* **1983**, *48*, 321.

(13) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2920; **1982**, 271, 1029.

(14) McKillop, A.; Hunt, J. D.; Zelesko, M. J.; Fower, J. S.; Taylor, E. C.; McGillivray, G. M.; Kienzle, F. *J. Am. Chem. Soc.* **1971**, *93*, 4841.

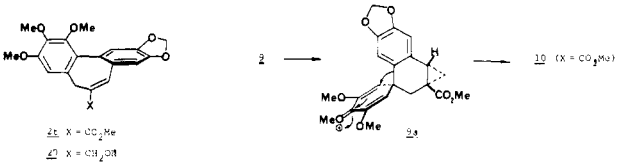


conversion of **25** into the biaryl **10** (X = CO_2Me) in low yield. Treatment of **24** with $PdCl_2$/AcOH/AcONa/90 °C did not give any biaryl **10** (X = CO_2Me).[15]

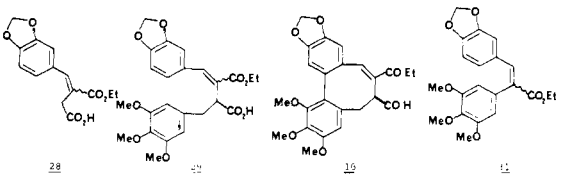
Since it is known that arylthallation is a reversible electrophilic substitution reaction, an obvious recourse was to conduct the $Tl(OCOCF_3)_3$ oxidation in strongly acidic media in order to protonate **24** reversibly, and subsequent irreversible oxidation of **17** to **10** (X = CO_2Me) should convert **24** into **10** (X = CO_2Me). In this way, we arrived at the conditions (neat TFA) that gave the required biaryl **10** (X = CO_2Me) in 43% yield.

It should be noted that at this stage, we did not know the relative configuration of the biaryl twist in **10** (X = CO_2Me) with respect to the cyclopropane, other than **10** (X = COMe), was a single compound.

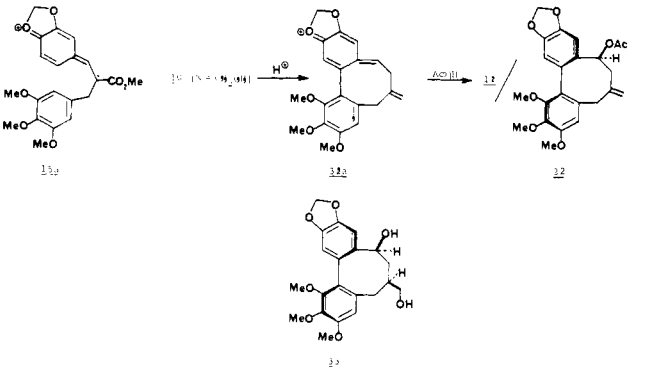
During the $Tl(OCOCF_3)_3$ oxidation of **17** to **10** (X = CO_2Me), we isolated a small quantity (ca. 2%) of a highly fluorescent compound assigned the structure **26**. Since the R_f's of **14** and **16** are virtually identical, apparently a small amount of unreacted **14** was converted into the methyl ester **15** and exposed to the $Tl(OCOCF_3)_3$ procedure to give the allocolchicine derivative **26**.[17] To test that this was the case, the phosphonate **13** was treated with NaH/DME/piperonal/20 °C to give the (*E*)-α,β-unsaturated ester **15** (91.5%) (containing less than 5% of the *Z* isomer). When the solution of **15** in TFA at −18 °C was treated with $Tl(OCOCF_3)_3$ (1.15 equiv) the biaryl **26** was isolated after chromatography in 81% yield. This yield is approximately twice that normally associated with non-phenolic oxidations in the steganone lignan area.[5,6] To correlate **26** with the biaryl **10** (X = CO_2Me), **26** was reduced with $LiAlH_4$ to give the allylic alcohol **27** (71%) and exposed to the Simmons–Smith cyclopropanation conditions Zn/Cu/CH_2I_2/Et_2O to provide the cyclopropylcarbinol **10** (X = CH_2OH) (74%). The stereochemistry depicted for **10** (X = CH_2OH) is based upon cyclopropanation from the least-hindered face of the allylic double bond opposite the trimethoxybenzene ring in **27**. Reduction of **10** (X = CO_2Me) with $LiAlH_4$ gave **10** (X = CH_2OH) identical with the material prepared by the above route. Consequently, we can assign **10** (X = CO_2Me) the stereochemistry shown. The spirodiene intermediate **9a** accounts for the stereochemical result and is considerably less hindered than the cyclopropane epimer.



The preferred route to **10** (X = CH_2OH) is via the cinnamate **15** and allocolchicine derivative **26**. It was of some interest to examine whether or not other simple cinnamate derivatives could be oxidized in a similar fashion. In particular, is it possible to produce an eight-membered ring directly? The dianion of the Stobbe condensation product **28** was treated with 3,4,5-trimethoxybenzyl bromide to give **29**. Exposure of **29** to $Tl(OCOCF_3)_3$ under a number of conditions did not give any of the desired eight-membered ring adduct **30**; instead, only arylthallation resulted. Similarly, the stilbene derivative **31** did not give the corresponding phenanthrene compound on treatment with $Tl(OCOCF_3)_3$.



It was established that the geometry of the double bond in **15** does not drastically affect the oxidation to **10** (X = CO_2Me). In a separate series of experiments, pure (*E*)-**15** was converted into **10** (X = CO_2Me) (70%) by using the $Tl(OCOCF_3)_3$ procedure, and pure (*Z*)-**15** was also converted into **10** (X = CO_2Me) (28%).



The stereoconvergent nature of the oxidative coupling reaction was shown to be the result of acid-catalyzed (TFA) equilibration of *E* and *Z* isomers, rather than oxidation of the cinnamate **15** to the radical cation **15a**.

In order to complete the synthesis the seven-membered ring, adduct **10** (X = CO_2Me) must be expanded to an eight-membered ring. Treatment of **10** (X = CO_2Me) with a variety of electrophiles did not initiate ring expansion, whereas treatment of **10** (X = CH_2OH) with AcOH/AcONa/$HClO_4$/45 °C for 3h gave **32** (97%) as a single stereoisomer.[10] It is not clear whether or not inversion or retention of configuration at C-8 has taken place. While an extensively delocalized carbonium such as **32a** predicts retention of configuration, since acetate anion would be expected to quench **32a** from the underside opposite the trimethoxyaryl ring to give **11**, it creates substantial strain in the intermediate ion **32a**. A more plausible alternative is a concerted reaction that results in inversion at C-8 to give **32**. It should also be noted that the stereochemistry at C-8 is removed in the process of transforming the oxoacid **7** into steganone **4**.[3] The correct relative configuration between C-6 and the biaryl twist was established by hydroboration BH_3/THF/0 °C followed by H_2O_2/NaOH and hydrolysis K_2CO_3/H_2O/MeOH to give the diol **33** as a single stereoisomer. To unequivocally establish the stereochemistry of C-6 with respect to the biaryl twist, **35** was oxidized by using Jones reagent at 20 °C to give the known oxoacid **7** (80%), which on treatment with diazomethane gave the ester **7a**, mp 132.5–136 °C (from MeOH) (lit.[3,5] mp 133–134 °C). The oxoacid **7** was converted into (±)-steganone (**4**) by using standard conditions (5% KOH/37% CH_2O, followed by Jones oxidation) and was identical with an authentic sample kindly supplied by Dr. A. T. Sneden from the collection of the late Prof. S. M. Kupchan.

The synthesis of the oxoacid **7** produces the correct relative configuration between the C-6 substituent and the biaryl twist, whereas the other syntheses[18] produce the isomeric oxoacid **6** and

(15) Uemura, S.; Ikeda, Y.; Ichikawa, K. *Chem. Commun.* **1971**, 390.
(16) Roberts, R. M. G. *Tetrahedron* **1980**, *36*, 3281. See also ref 9.
(17) Santa<<acyvy, F. *Helv. Chim. Acta* **1948**, *31*, 821. Fernholz, H. *Ann.* **1950**, *568*, 63. Ford, W. T.; Mewcomb, M. *J. Am. Chem. Soc.* **1973**, *95*, 6277.

(18) For other syntheses of steganone and isosteganone, see: Krow, G. R.; Damodaran, K. M.; Michener, E.; Wolf, R.; Guare, J. *J. Org. Chem.* **1978**, *43*, 3950. Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *Ibid.* **1976**, *41*, 3773. Brown, E.; Dhal, R.; Robin, J.-P. *Tetrahedron* **1983**, *39*, 2787. Tomioka, K.; Mizuguchi, H.; Koga, K. *Tetrahedron Lett.* **1979**, 1409. Tomioka, K.; Ishiguro, T.; Koga, K. *Ibid.* **1980**, 2973. Merič, M.; Ben-David, Y.; Ghera, E. *Ibid.* **1981**, 5091. Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1979**, 652. Robin, J.-P.; Gringpore, O.; Brown, E. *Tetrahedron Lett.* **1980**, 2709. All structures are represented by a single enantiomeric form to depict racemic compounds. The correct absolute configuration of **4** was correctly determined by Koga and is antipodal to the enantiomers drawn in this paper.

convert it into isosteganone **5**, which thermally isomerizes to steganone (**4**). The synthesis of the oxoacid **7** from piperonal proceeds in nine steps in an overall yield of 24%.

Experimental Section

(*E*)- and (*Z*)-*tert*-Butyl 2-[3,4-(Methylenedioxy)benzylidene]-3-(3,4,5-trimethoxyphenyl)propanoate (14). *tert*-Butyl diethylphosphonoacetate (1.00 g, 4 mmol) in dry glyme (15 mL) at 0 °C was treated with NaH (100 mg, 98%), followed by 3,4,5-trimethoxybenzyl bromide (1.04 g, 4 mmol) in glyme (10 mL). After 1 h at 25 °C, additional NaH (170 mg) was added, the mixture cooled at 0 °C, and piperonal (600 mg, 4 mmol) in glyme (10 mL) added. The above solution was quenched after 0.5 h with 5% aqueous $NaHSO_3$ (100 mL) and extracted with EtOAc (4 × 30 mL). The dried (Na_2SO_4) extract was evaporated in vacuo, and the reside was purified by flash chromatography over silica gel eluting with EtOAc/petrol (9:1) to give **14** (650 mg, 38% based on piperonal): mp 93–96 °C (*E* isomer crystallized from light petroleum); IR (thin film) 1700, 1585, 1240, 1155, and 1125 cm^{-1}; NMR δ 7.7 (1 H, s), 6.7–6.9 (3 H, m), 6.4 (2 H, d), 5.9 (2 H, s), 3.8 (9 H, 3s), 3.8 (2 H, s), 1.4 (9 H, s). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.41; H, 6.38. Found: C, 67.27; H, 6.59%.

***cis*-*tert*-Butyl 1-(3,4,5-Trimethoxybenzyl)-2-[3,4-(methylenedioxy)-phenyl]cyclopropanecarboxylate (16).** Dimethylsulfoxonium methylide (3.0 equiv generated from trimethylsulfoxonium iodide and NaH) in dry Me_2SO (20 mLe) at 20 °C was treated with the ester **14** (3.4 g) in Me_2SO (10 mL). The mixture was stirred for 2 h at 20 °C and then 15 h at 60 °C. The solution was concentrated under vacuum to ca. 10 mL and quenched with saturated aqueous NH_4Cl solution. The product was extracted with EtOAc (5 × 20 mL), and the extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo and flash chromatography of the residue over silica gel gave **16** (2.72 g, 81.6%): mp 103–105 °C (from ether/petrol); IR 1705, 1590, 1500, 1485, 1230, 1210, 1120 cm^{-1}; NMR δ 6.7 (3 H, br s), 6.3 (2 H, br s), 5.9 (2 H, s), 2.7 (1 H, t), 2.5 (2 H, ABq, $\Delta\nu$ = 84, J = 15 Hz), 1.7 (1 H, d of d), 1.1 (1 H, d of d); MS *m/e* $C_{25}H_{30}O_7$ 442 M − CH) 429 (12), 428 (45), 373 (22), 372 (100), 371 (21), 353 (17), 311 (20). No parent ion was observed.

***cis*-Methyl 1-(3,4,5-Trimethoxybenzyl)-2-[3,4-(methylenedioxy)-phenyl]cyclopropanecarboxylate (17).** To a solution of the *tert*-butyl ester **16** (1.1 g) in toluene (20 mL) was added *p*-TsOH (5 mg) and the mixture heated at reflux for 10 h. The solvent was evaporated and the residue purified by flash chromatography, eluting with 80% $CHCl_3$/20% petrol to give the acid **18a** (R = OH) (720 mg, 76%): mp 168–169 °C (from benzene/petrol); IR 3600–2500 (br, OH), 1690, 1590, 1490; NMR δ 10.2 (1 H, br), 6.85 (3 H, m), 6.5 (2 H, s), 3.95 (9 H, s), 2.97 (1 H, t, J = 8 Hz), 2.6 (2 H, ABq, J = 15 Hz, $\Delta\nu$ = 250), 1.95 (1 H, d of d, J = 5, 12 Hz), 1.45 (1 H, t, J = 5 Hz), MS, *m/e* calcd. for $C_{21}H_{22}O_7$ 386 (46), 302 (11), 301 (56), 251 (11), 181 (100). A solution of the above acid **18a** (R = OH) (310 mg, 0.81 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with excess diazomethane to give **17** (295 mg 92%); IR 1709, 1585, 1482, 1425; NMR δ 6.8 (3 H, m), 6.4 (2 H, s), 6.0 (2 H, s), 3.85 (9 H, s), 3.75 (3 H, s), 2.85 (1 H, t, J = 8 Hz) 2.6 (2 H, ABq, J = 12 Hz, $\Delta\nu$ = 240), 1.85 (1 H, d of d, J = 5, 10 Hz), 1.3 (1 H, t, J = 8 Hz); MS, *m/e* calcd for $C_{22}H_{24}O_7$ 400 (39), 386 (21), 326 (10), 301 (36), 181 (100).

Methyl 2,3-(Methylenedioxy)-8,9,10-trimethoxydibenzo[*a*,*c*]cyclopropa[*e*]cycloheptane-5$\alpha\beta$(4bβH)-carboxylate (10) (X = CO_2Me). To a solution of the cyclopropyl ester **17** (350 mg) in dry TFA (8 mL) at −18 °C under argon was added thallium tris (trifluoroacetate) (550 mg) in one portion with rapid stirring. The dark green mixture was left between −15 and −18 °C for 25 min and then quenched with water (40 mL). The solution was extracted with EtOAc (4 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo to give a residue that was purified by flash chromatography over silica gel, eluting with 10% EtOAc/90% petrol to give **10** (R = CO_2Me) (150 mg, 43%): mp 136–138 °C (from EtOAc/hexane); IR ($CHCl_3$) 1710, 1600, 1465, 1130, 1100, and 1030 cm^{-1}; NMR (360 MHz) δ 0.97 (1 H, dd, J = 4.2, 3.3 Hz), 1.48 (1 H, dd, J = 4, 9.4 Hz), 2.60 (1 H, dd, J = 5.7, 9.3 Hz), 2.75 (2 H, ABq, J = 13.7 Hz, $\Delta\nu_{AB}$ = 444), 3.62 (3 H, s), 3.63 (3 H, s), 3.90 (6 H, s), 5.96 (2 H, ABq, J = 1.3 Hz, $\Delta\nu_{AB}$ = 8), 6.78 (1 H, s), 6.91 (1 H, s), 6.93 (1 H, s); MS, *m/e* calcd for $C_{22}H_{22}O_7$ 398.136, found 398.136.

When the TFAA oxidation was carried out in CCl_4/TFA (9:1) and the reaction mixture worked up with KI (1 g)/I_2 (200 mg)/H_2O (10 mL), the iodide **25** (40 mg, from 40 mg of **17**, representing a 76% yield) was isolated.

A solution of the iodide **25** (10 mg) in acetonitrile (8 mL) was irradiated in a Pyrex tube using a 450-W high-pressure mercury lamp. Slow conversion into **10** (R = CO_2Me) was observed.

Treatment of **17** with VOF_3 or $FeCl_3$ gave the tetralin derivative **23**: NMR δ 6.6–6.8 (3 H, m), 6.4 (1 H, s), 5.9 (2 H, s), 4.2 (1 H, t), 3.85–4.9 (9 H, 3s), 3.2 (3 H, s), 3.09 (2 H, ABq, J = 16 Hz, $\Delta\nu$ = 209), 3.05 (1 H, 5s), 2.25 (1 H, m), 2.05 (1 H, t).

(*E*)-Methyl 2-[3,4-(Methylenedioxy)benzylidene]-3-(3,4,5-trimethoxyphenyl)propanoate (15). To a solution of the phosphonate **13** (100 mg, 0.256 mmol) in DME (5 mL was added NaH (13 mg) at 0 °C followed by piperonal (38 mg). After 12 h at 20 °C, the mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and evaporated to give the crude product, which chromatographed over silica gel, eluting with 20% EtOAc/petrol to give **15** (88 mg, 91.5%) as thick oil: IR (thin film) 1700, 1585, 1490, 1230, and 1120 cm^{-1}; NMR (90 MHz) δ 7.8 (1 H, s), 6.7–6.9 (3 H, m), 6.3–6.4 (2 H, m), 5.9 (2 H, s), 3.7–3.8 (9 H, 3s), 3.6 (2 H, s). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.41; H, 5.84.

Methyl 2,3-(Methylenedioxy)-9,10,11-trimethoxydibenzo[*a*,*c*]cycloheptene-6-carboxylate (26). To a solution of **15** (3.03 g) in TFA (39.2 mL) at −18 °C was added thallium tris(trifluoroacetate) (4.9 g) in one portion. After 0.5 h at −18 °C, the mixture was quenched with ice water (100 mL) and extracted with EtOAc (200 mL). The extract was washed with brine (2 × 100 mL), dried ($MgSO_4$), and evaporated and toluene added. Evaporation in vacuo and chromatography of the residue over silica gel eluting with 10% EtOAc/petrol gave **26** (2.48 g 81%), as a colorless foam: IR ($CHCl_3$) 1695, 1590, 1480, 1400, 1270, 1100, and 1033 cm^{-1}; UV (EtOH) max 203, 252 nm (ϵ 3.74 × 10^4, 3.42 × 10^4); NMR (360 MHz) δ 7.49 (1 H, br s), 7.32 (1 H, s), 6.85 (1 H, s), 6.65 (1 H, s), 6.04 (2 H, ABq, J = 1 Hz, $\Delta\nu_{AB}$ =21), 3.89 (3 H, s), 3.87 (3 H, s), 3.80 (3 H, s), 3.23 (2 H, ABq, J = 13 Hz, $\Delta\nu_{AB}$ = 400), 3.49 (3 H, s). Anal. Calcd for $C_{21}H_{20}O_7$; C, 65.62; H, 5.24. Found: C, 65.43; H, 5.29.

2,3-(Methylenedioxy)-9,10,11-trimethoxydibenzo[*a*,*c*]cycloheptenyl-6-carbinol (27). To the ester **26** (1.857 g, 4.83 mmol) in THF (10 mL) at −78 °C was added $LiAlH_4$ (183 mg) and the mixture warmed to 0 °C. Workup in the standard manner gave **27** (1.22 g after recrystallization from benzene, 71%): mp 152–153 °C (from benzene); IR ($CHCl_3$) 3600, 2980, 2920, 2880, 2820, 1590, 1490, 1470, 1400, 1130, 1090, and 1030 cm^{-1}; NMR (360 MHz) δ 6.75 (1 H, s), 6.55 (1 H, s), 6.34 (1 H, br s), 5.9 (2 H, d, $\Delta\nu$ = 23), 4.29 (2 H, br s), 3.87 (3 H, s), 3.85 (3 H, s), 3.49 (3 H, s), 2.90 (2 H, ABq, J = 13 Hz, $\Delta\nu$ = 98), 1.78 (1 H, br s exchanged by D_2O). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.47; H, 5.41.

2,3-(Methylenedioxy)-8,9,10-trimethoxydibenzo[*a*,*c*]cyclopropa[*e*]-cycloheptyl-5aβ(4bβH)-carbinol (10) (X = CH_2OH). To a freshly prepared Zu(Cu) couple (552 mg, 2.75 equiv) in Et_2O (3 mL) was added I_2 (5 mg), the mixture heated at reflux for 1 min, and CH_2I_2 (538 mL 2.15 eq) added over 3 min. After heating at reflux for 45 min, a solution of **27** (1.1 g) in toluene (7 mL) was added and the mixture refluxed for 1 h. The cooled mixture was quenched with water (6 mL) and extracted with CH_2Cl_2 (20 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue chromatographed over silica gel, eluting with 1:1 EtOAc/hexane to give **10** (X = CH_2OH) (847 mg, 74%): mp 153–154 °C (from Et_2O/petrol); IR ($CHCl_3$) 3600, 3450, 1590, 1480, 1450, 1400, and 1320 cm^{-1}; NMR δ 6.93 (1 H, s), 6.89 (1 H, s), 6.65 (1 H, s), 5.95 (2 H, d with each peak finely split, $\Delta\nu$ = 9), 3.90 (6 H, s), 3.72 (1 H, lower half of an ABq centered at 2.92, $\Delta\nu$ = 579, J = 11 Hz), 3.63 (3 H, s), 2.95 (1 H, AQb, $\Delta\nu$ = 29, J = 13.5 Hz), 2.12 (1 H, upper half of an ABq centered at 2.92, $\Delta\nu$ = 579, J = 11 Hz), 1.67 (1 H, d of d, d_1 = 4, d_2 = 9), 1.45 (OH, br), 0.95 (1 H, d of d, d = 4.4, d_2 = 9), 0.66 (1 H, t with each peak split further, J = 4.3 Hz); MS, *m/e* calcd for $C_{21}H_{22}O_6$ 370.142, found 370.141.

Treatment of the ester **10** (X = CO_2Me) (75 mg) in ether (5 mL) with $LiAlH_4$ (50 mg) in ether (2 mL) at 0 °C for 10 min gave the carbinol **10** (X = CH_2OH) (35 mg, 75%), identical in all respects with the material made through the Simmons–Smith cyclopropanation route.

5,7,8-Trihydro-1,2,3-trimethoxy-10,11-(methylenedioxy)-6-methylene-8β-acetoxydibenzo[*a*,*c*]cyclooctene (32). The cyclopropylcarbinol **10** (X = CH_2OH) (239 mg) in AcOH (3 mL) containing NaOAc (100 mg) and $HClO_4$ (10 drops) was heated at 45 °C for 3 h, poured onto powdered Na_2CO_3, and lyophilized to remove AcOH. The residue was treated with water (10 mL), $CHCl_3$ (30 mL), and solid Na_2CO_3 until the aqueous phase was basic. The aqueous phase was further extracted with $CHCl_3$, and the combined extracts were dried ($MsSO_4$) and evaporated in vacuo. The residue was chromatographed over silica gel eluting with 20% EtOAc/petrol to give **32** (99 mg, 37%) and the unrearranged acetate derived from **10** (X = CH_2OH), namely **10** (X = CH_2OAc) (159 mg, 60%). The yield of **32** is 97% based upon the recovery of **10** (X = CH_2OAc), which can be converted into **32** by the above solvolysis conditions. It should be noted that prolonged solvolysis decreases the yield of **32**. The compound **32** has mp 148–149.5 °C: IR ($CHCl_3$) 1730, 1590, and 1480 cm^{-1}; NMR δ 7.0 (1 H, s), 6.75 (1 H, s), 6.6 (1 H, s), 6.0 (2 H, d, J = 6 Hz), 5.3 (1 H, m), 5.0 (1 H, br s), 4.82 (1 H, br s), 3.9 (6 H, 2s), 3.8 (3 H, s), 3.15 (1 H, lower half

of ABq, J = 12 Hz), 2.55–2.75 (3 H, br m), 2.0 (3 H, s). Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 67.11; H, 5.99.

5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-(methylenedioxy)-8β-hydroxydibenzo[a,c]cyclooctenyl-6β-carbinol (33). To a solution of **32** (252 mg, 0.61 mmol) in THF (1.2 mL) at 0 °C was added a solution of BH_3·THF (3.12 mL, 0.98 M) and the mixture warmed to 20 °C. After 0.5 h, the solution was cooled to 0 °C and 3 N NaOH (4 mL) added, followed by 30% H_2O_2 (4 mL), and stirred at 20 °C for20 min, and saturated with solid K_2CO_3. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL, dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in MeOH (3 mL) and water (3 mL), and K_2CO_3 was (400 mg) added. After 12 h at 20 °C, the mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL) and CH_2Cl_2 (2 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was stirred with powdered K_2CO_3 (400 mg) in 1:1 MeOH–H_2O (6 mL) for 12 h at room temperature, diluted with water, extracted with ethyl acetate (10 mL) and methylene chloride (20 mL), and dried ($MgSO_4$) and the solvent evaporated to give **33** (219 mg, 92.4%). Recrystallization gave pure **33**, mp 191–192 °C (from benzene/chloroform), 190 mg, 80%: IR ($CHCl_3$) 3600, 1590, 1486, 1140, 1100, and 1035 cm^{-1}; NMR (360 MHz) δ 7.16 (1 H, s), 7.08 (1 H, s), 6.6 (1 H, s), 6.55 (1 H, s), 5.90 (2 H, d, J = 10 Hz), 4.3 (1 H, d, J = 10 Hz), 3.8 (6 H, s), 3.6 (3 H, s), 2.8 (1 H, m), 2.3 (1 H, d, J = 13 Hz), 2.1 (1 H, br m), 2.0 (1 H, d, J = 13 Hz), 1.8 (2 H, br m). Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.99; H, 6.27.

Methyl 5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-(methylenedioxy)-8-oxodibenzo[a,c]cyclooctene-6β-carboxylate (7a). To a solution of the diol **33** (190 mg, 0.49 mmol) in acetone (10 mL) was added freshly prepared Jones reagent (0.35 mL of a solution prepared from 1.34 g of CrO_3/1.2 of mL 6 N H_2SO_4 in 10 mL of H_2O). After 2.5 h at 20 °C, the mixture was quenched with MeOH and worked up in the standard manner to give the oxoacid **7** (157 mg, 80%): NMR (360 MHz) δ 7.68 (1 H, s), 6.67 (1 H, s), 6.55 (1 H, s), 6.07 (2 H, d, J = 9 Hz), 3.92 (3 H, s), 3.83 (3 H, s), 3.58 (3 H, s), 3.16 (1 H, ABq centered at 2.98, J = 13.7 Hz, $\Delta\nu_{AB}$ = 134), 3.05 (1 H, br m), 2.85 (1 H, t, J = 7 Hz), 2.8 (1 H, dd, J = 14, 1 Hz), 2.62 (1 H, t, J = 13 Hz).

To a solution of the oxoacid **7** (157 mg) in ether (10 mL) was added excess ethereal diazomethane at 0 °C. Evaporation and chromatography over silica gel, eluting with petrol–EtOAc (4:1), gave the oxo ester **7a** (115 mg, 70%): mp 132.5–136 °C (from MeOH) [lit.[3] 133–134 °C]; NMR δ 7.67 (1 H, s), 6.66 (1 H, s), 6.45 (1 H, s), 6.05 (2 H, d, J = 11 Hz), 3.91 (3 H, s), 3.85 (3 H, s), 3.71 (3 H, s), 3.56 (3 H, s), 3.13 (1 H, lower half of ABq, J = 14 Hz), 3.0 (1 H, m), 2.8 (2 H, m), 2.6 (1 H, t, J = 13 Hz).

(±)-Steganone (4). Oxoacid **7** (46 mg) was stirred with 5% KOH (1 mL) and 37% CH_2O (0.2 mL) for 2 **h**. The mixture was acidified with 3 N HCl, extracted with $CHCl_3$ (3 × 5 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was taken up in acetone (3 mL) and at 0 °C; Jones reagent was added until the orange persisted. Excess Jones reagent was destroyed with MeOH. Water was added, and the mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined chloroform extracts were washed with 1 N NaOH. The $CHCl_3$ solution was dried ($MgSO_4$) and the solvent removed to afford (±)-steganone (**4**) (8 mg 17%). Recrystallization from CH_2Cl_2–EtOH provided material melting at 226–229 °C. The spectral characteristics of this material were indentical, with the exception of rotation, with a sample of natural (±)-steganone.

Acknowledgment. We thank the National Institutes of Health (GM-29801) for their financial support of part of this work. The National Science Foundation is thanked for financial assistance in purchasing high-field NMR equipment (CHE 81-05004).

Registry No. (±)-**4**, 58800-45-6; (±)-**7**, 65310-09-0; (±)-**7a**, 65310-11-4; (±)-**10** (X = CO_2Me), 97253-43-5; (±)-**10** (X = CH_2OH), 95238-10-1; (±)-**10** (X = CH_2OAc), 97253-47-9; (±)-**13**, 97253-46-8; (*E*)-**14**, 97253-38-8; (*Z*)-**14**, 97253-39-9; (*E*)-**15**, 95238-06-5; (*Z*)-**15**, 95238-07-6; (±)-**16**, 97253-40-2; (±)-**17**, 97253-42-4; (±)-**18**, 97253-50-4; (±)-**18a**, 97253-41-3; **19**, 61833-23-6; (±)-**20**, 97253-48-0; (±)-**21**, 97253-49-1; (±)-**22**, 97277-60-6; **23**, 97253-45-7; (±)-**24**, 97293-66-8; (±)-**25**, 97253-44-6; (±)-**26**, 95238-08-7; (±)-**27**, 95238-09-8; (±)-**32**, 95238-11-2; (±)-**33**, 95238-12-3; *tert*-butyl diethylphosphonoacetate, 27784-76-5; 3,4,5-trimethoxybenzyl bromide, 21852-50-6; piperonal, 120-57-0; dimethylsulfoxonium methylide, 5367-24-8.

Supplementary Material Available: Experimental details for **19–22** (2 pages). Ordering information is given on any current masthead page.