pecifically benz[b]xanthen-12-ones. The sulfone **4c**, which serves as a synthon for the A and B rings, was prepared from the amide **2**.[12] Lithiation of **2** (*sec*-butyllithium, TMEDA), followed by reaction with DMF, furnished the aldehyde **3** (mp 91–2 °C, lit.[12] mp 92–4 °C; 56%), which was hydrolyzed ($HCl/HOAc/H_2O$) to the phthaldehydic acid **4a** (mp 214–15 °C; 81%). Heating **4a** with benzenethiol in benzene and a catalytic amount of toluenesulfonic acid gave the sulfide **4b** (mp 124–125 °C; 91%), which was oxidized ($MCPBA/CH_2Cl_2$) quantitatively to the sulfone **4c** (mp 175–176 °C).

Condensation of the anion of **4c** with the chromone **5**[13] (LiO-*t*-Bu, THF, −78 °C to room temperature, and then brief reflux) furnished **6** regiospecifically in 27% yield.[14] Oxidation of **6** with Fetizon reagent[15] (Ag_2CO_3/Celite) produced the quinone **7** (91%) with the same physical and spectral properties as those given in the literature. Demethylation of **7** with LiI in DMF[9] (78%) gave bikaverin (**1**), identical[16] with an authentic sample.

The accomplished preparation of **1** is much shorter than those reported previously,[9-11] is achieved in better overall yield, and is amenable to the synthesis of a variety of analogues. The use of chromone as a Michael acceptor expands the utility of the sulfone annelation[1] for regiospecific preparation of polycyclic aromatic ring systems. We are currently utilizing this reaction to prepare other natural products containing a xanthenone fragment.

Acknowledgment. We express our appreciation to Dr. Ryback for providing an authentic sample of Bikaverin. This work was generously supported by the National Cancer Institute of the National Institutes of Health under grant CA 18141.

(11) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. Condensation of (phenylsulfonyl)isobenzofuranones has been widely used by us and by others to achieve regiospecific total syntheses of naturally occurring polycyclic aromatic systems. For an extensive list, see ref 9 in: Hauser, F. M.; Baghdanov, V. M. *Tetrahedron* **1984**, *80*, 4719.

(12) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183.

(13) The chromone **5** was prepared by sodium hydride condensation of 2-hydroxy-4-methoxy-6-methylacetophenone with ethyl formate. The diketone intermediate was cyclized to the chromone with trifluoroacetic acid and trifluoroacetic anhydride. For a similar preparation, see: Ahlumalia, V. K.; Chanandra, P. *Indian J. Chem.* **1977**, *15b*, 331.

(14) Much better yields of benz[b]xanthen-12-ones are obtained from condensation of less highly substituted (phenylsulfonyl)isobenzofuranones and chromones. For example, condensation of chromone with 7-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone gave the corresponding methoxybenzxanthen-12-one in 65% yield.

(15) Fetizon, M.; Golfier, M. *C. R. Seances Acad. Sci.* **1968**, *267*, 900.

(16) The infrared and ^1H NMR spectral properties of the synthetic and authentic materials were identical.

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Ruthenium(IV) Dioxide in Fluoro Acid Medium: An Efficient Biaryl Phenol Coupling Process, Exemplified with a Biomimetic Access to the Skeleton of Steganacin from Presteganes[1,2]

Summary: Ruthenium(IV) dioxide dihydrate in fluoro acids was found to be very efficient for the oxidative phenol coupling of presteganes **1a** and **1b** to give the corresponding bisbenzocyclooctadiene lactones **2a** and **2b**, closely related to the antitumor lignan steganacin. The same conditions applied to the mammalian lignan enterolactone **1e** were ineffective. Ultrasound assistance and use of the triflic acid–triflic anhydride–boron trifluoride medium at room temperature were found to be the best conditions.

Sir: Bridged biaryls related to the well-known classes of natural products of high pharmaceutical interest are widely distributed in higher plants.[3] Their biogenesis always involves enzymic intramolecular biaryl oxidative coupling of phenolic precursors via radical cations, as a key step (Scheme I). So, an improvement of both the efficiency and selectivity of the biomimetic synthetic methods providing access to these skeletons would be very useful.

Kupchan[4] and, more recently, Taylor and McKillop[5] have improved the sluggish known methods[6] by using vanadium(V) oxyhalides and thallium(III) tris(trifluoroacetate) (TTFA), respectively. Unfortunately, the yield of phenolic coupling, which is the real mechanism used by nature, generally remains poor to medium in the laboratory.

As a part of our continuing work in the isolation and the synthesis of potential antitumor and antiviral drugs, effort was devoted to the development of an efficient route to the above mentioned classes of natural substances. Recently we described that ruthenium(IV) dioxide in TFA–TFAA medium is a versatile reagent for the synthesis of bridged biaryls from *nonphenolic* precursors.[7] In the present work, we attempted to determine whether the title reagent could be employed for an efficient biomimetic synthesis of bisbenzocyclooctadiene lactones closely related to the antitumor lignan steganacin by oxidative coupling

(1) Presented at the 30th National Organic Symposium of the American Chemical Society, Vancouver, June 22, 1987. The present paper is dedicated to the late S. M. Kupchan.

(2) Part of thesis of Y. L.

(3) Including the following. (a) **Alkaloids.** Antitumor aporphines, e.g., thalicarpine: Hussain, S. F.; Freyer, A. J.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 494. Homoaporphines: Castro, J. L.; Castedo, L.; Riguera, R. *Tetrahedron Lett.* **1985**, *26*, 1561. Azahomoaporphines: Cassels, B. K.; Cavé, A.; Davoust, D.; Hocquemiller, R.; Rasamizafy, S.; Tadic, D. *J. Chem. Soc., Chem. Commun.* **1986**, 1481. Antitumor phenanthroquinolizidines, e.g., cryptopleurine: Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412. Antiviral phenanthroindolizidines, e.g., tylophorine: Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50. Dibenzazecines: Aladesanmi, A. J.; Kelley, C. J.; Leary, J. D. *J. Nat. Prod.* **1983**, *46*, 127. Dibenzazonines: Kupchan, S. M.; Kim, C. K. *J. Am. Chem. Soc.* **1975**, *97*, 5623. Antitumor tropolones, e.g., Colchicine: Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4594. Antitumor benzodihydrophenanthridines, e.g., nitidine: Zee-Cheng, R. K. I.; Cheng, C. C. *J. Med. Chem.* **1975**, *18*, 66. (b) **Lignoids.** Dimethylbisbenzocyclooctadienes, e.g., schizandrins: Takeya, T.; Okubo, T.; Nishida, S.; Tobinaga, S. *Chem. Pharm. Bull.* **1985**, *33*, 3599. Bisbenzocyclooctadiene lactones, e.g., steganacin: Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. V.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 335. Robin, J.-P.; Davoust, D.; Taafrout, M. *Tetrahedron Lett.* **1986**, *27*, 2871. (c) **Dihydrophenanthrenes.** Cytotoxic juncusol: Kende, A. S.; Curran, D. P. *Tetrahedron Lett.* **1978**, *33*, 3003.

(4) Kupchan, S. M.; Liepa, A. J.; Kameswaran, V.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 6861.

(5) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513.

(6) (a) For a review on phenol coupling, see: Taylor, W. I.; Battersby, A. R. "Oxidative Coupling of Phenols"; Marcel Dekker: New York, 1967. (b) For an exhaustive recent review on radical ion biaryl coupling, see: Kovacic, P.; Jones, M. B. *Chem. Rev.* **1987**, *87*, 357 and reviews cited herein (including Lewis acid–oxidant combinations, phenolic coupling, intramolecular couplings, and so on).

(7) Including (a) Lignans pertaining to the steganacin group: Landais, Y.; Robin, J. P. *Tetrahedron Lett.* **1986**, *27*, 1785. (b) Neolignans of the schizandrin group: Landais, Y.; Lebrun, A.; Robin, J. P. *Tetrahedron Lett.* **1986**, *27*, 5377. (c) Aporphinic, homoaporphinic, and azafluoranthene alkaloids: Landais, Y.; Rambault, D.; Robin, J. P. *Tetrahedron Lett.* **1987**, *28*, 543 and references cited herein.

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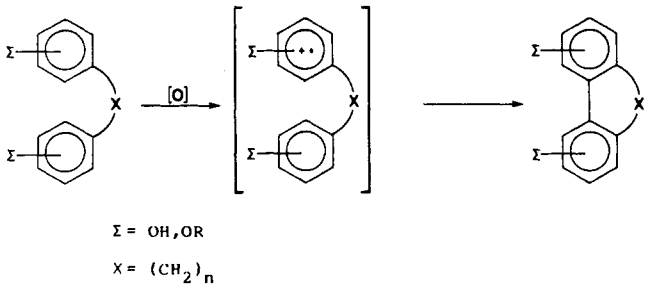
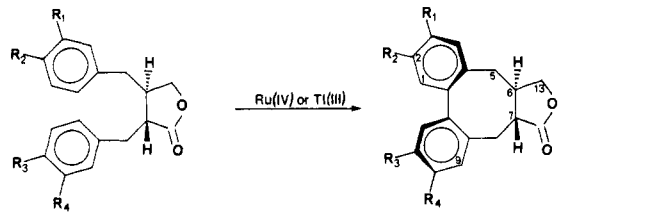
Scheme I



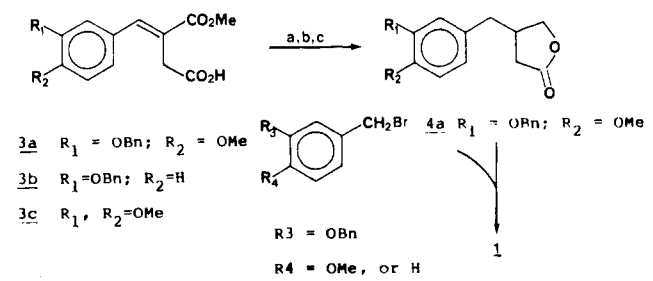
Scheme II



1a $R_1=R_2=R_3=$ OMe; $R_4=$ OH
1b $R_2=R_3=$ OMe; $R_1=R_4=$ OH
1c $R_1=R_4=$ OBn; $R_2=R_3=$ OMe
1d $R_1=R_2,R_3,R_4=$ OMe
1e $R_1=R_4=$ OH; $R_2=R_3=$ H
1f $R_1=R_4=$ OMe; $R_2=R_3=$ H

(M*, 6R*,7R*)-2
2a $R_1=R_2=R_3=$ OMe; $R_4=$ OH
2b $R_2=R_3=$ OMe; $R_1,R_4=$ OH
2c $R_1=R_2=R_3=R_4=$ OMe

Scheme III



3a $R_1=$ OBn; $R_2=$ OMe
3b $R_1=$OBn; R_2=H
3c R_1, R_2=OMe

of *phenolic* natural dibenzylbutanolide lignans—named prestegane A (**1a**) and prestegane B (**1b**) (Scheme II).[8]

For this purpose, readily available prestegane B[9] was synthesized by alkylating the anion of (3-*O*-benzylisovanillyl)butanolide (**4a**) with *O*-benzylisovanillyl bromide.[10] Preparation of the former was easily achieved according to the method formerly designed by one of us (J.P.R.).[11,12] The protected dibenzylbutanolide **1c** was subsequently debenzylated to give **1b**[13] in 38% overall yield from commercial isovanillin. Synthetic **1a** and **1b** were first coupled with ruthenium(IV) dioxide dihydrate in trifluoroacetic acid–trifluoroacetic anhydride–boron trifluoride at room temperature and second under the described conditions.[14] Surprisingly, Ru(IV) oxidation gave

Table I

entry	compd[a]	conditions[b]	time, h	yields,[c] %
1	**2a**	A	15	80
2	**2b**	A	14	82
3	**2a**	B	6	82
4	**2b**	B	6	80
5	**2a**	C	3	80
6	**2b**	C	3	84
7	**2a**	D	2	45
8	**2b**	D	2	50

[a] Added in CH_2Cl_2. [b] Conditions: (A) RuO_2, $2H_2O$ (1.5 equiv); CH_2Cl_2/TFA–TFAA; BF_3·Et_2O; 20 °C; (B) RuO_2, $2H_2O$ (1.5 equiv); CH_2Cl_2/TFA–TFAA; BF_3·Et_2O; 20 °C; ultrasound; (C) RuO_2, $2H_2O$ (1.5 equiv); triflic acid–triflic anhydride; BF_3·Et_2O; 20 °C; (D) Tl_2O_3 (1.5 equiv); CH_2Cl_2/TFA–TFAA; BF_3·Et_2O; 20 °C. [c] Yield in isolated pure compound.

the phenolic bisbenzocyclooctadienes cleanly in the 80–85% range yield for the two studied models, vs 45–50% for TTFA. It is particularly noteworthy that simple removal of suspended solid followed by evaporation afforded the pure coupled compounds in good yields.[15] In this manner **1a** and **1b** gave **2a** and **2b**, respectively, as crystalline solids.[16]

Preliminary careful examination, by high-resolution ^1H NMR, of the aliphatic vicinal coupling constants of the parent phenols clearly indicated both a trans-fused lactone and an "iso" biaryl atropoisomeric center.[17] In another respect, treatment of **2a** and **2b** with diazomethane afforded the unique compound **2c**, the aliphatic parts of which in ^1H NMR were superimposable with the latter. Finally, **2c** was shown to be identical with the compound resulting from nonphenolic coupling of di-*O*-methylmatairesinol (**1d**).[7a,18]

As in nonphenolic coupling, it was found that the present coupling is stereospecific, giving an "iso" = *M**,6*R**,7*R** stereoisomer.[19]

After these encouraging preliminary results, trifluoromethanesulfonic acid–trifluoromethanesulfonic anhydride medium was also successfully tried, giving 80–85% yield, and it was also found that ultrasonic assistance allowed the use of shorter reaction times (see Table I).[20]

Since enterolactone **1e**, which has been recently described in mammalian fluid, is the only other example of

(8) Isolated from *Steganotaenia araliacea*: (a) Taafrout, M.; Rouessac, F.; Robin, J. P. *Tetrahedron Lett.* **1983**, *31*, 3237. (b) Taafrout, M.; Rouessac, F.; Robin, J. P.; Davoust, D. *Tetrahedron. Lett.* **1984**, *37*, 4127.
(9) Presently the first synthesis of prestegane B.
(10) LDA or $LiN(SiMe_3)_2$/THF–HMPA, –80 °C, 120 min.
(11) Brown, E.; Robin, J. P.; Dhal, R. *J. Chem. Soc., Chem. Commun.* **1978**, 556. (a) Selective reduction ($Ca(BH_4)_2$) of the potassium salt of the ethylenic Stobbe hemiester gave the corresponding unsaturated lactone, which was (b) hydrogenated and (c) rebenzylated to afford the crystalline butanolide **4a**, mp 56–57 °C, in 48% overall yield (Scheme III).
(12) All compounds exhibited satisfactory analytical data.
(13) Identical with a natural sample: see ref 8b. For analytical description and synthesis of prestegane A, see ref 8a.
(14) TTFA in situ generated from Tl_2O_3.
(15) As previously pointed out, ruthenium(IV) derivatives are nontoxic, nonvolatile, and poorly soluble in organic media.
(16) **2b**: mp 228–230 °C; IR ν_{CO} 1781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (dd, 1 H, C-7–H, J = 12.9, 9.0 Hz), 2.20 (m, 1 H, C-6–H), 2.27 (dd, 1 H, C-8α–H, J = 13.3, 9.0 Hz), 2.35 (dd, 1 H, C-5β–H, J = 13.3, 9.5 Hz), 2.61 (d, 1 H, C-5α–H, J = 13.3 Hz), 3.13 (d, 1 H, C-8β–H, J = 13.3 Hz), 3.76 (dd, 1 H, C-13β–H, J = 8.6, 11.2 Hz), 3.88 (s, 6 H, 2 × OCH_3), 4.36 (dd, 1 H, C-13α–H, J = 8.2, 6.5 Hz), 5.60 (br s, 2 H, OH), 6.67 (s, 2 H, C-1–H, C-12–H), 6.77 (s, 1 H, C-4–H), 6.87 (s, 1 H, C-9–H). **2a**: mp 204–206 °C; IR ν_{CO} 1781, 1773 cm^{-1}. The aliphatic parts of both these compounds were superimposable and identical with the isostegane one.
(17) Confirmed by the observation of the H-8β,H-7 coupling constant which was 0 Hz, corresponding to an H-8β/C-8/C-7/H-7 dihedral angle of 90°; see also: Robin, J. P.; Davoust, D.; Taafrout, M. *Tetrahedron Lett.* **1986**, *27*, 2971 and references cited herein.
(18) Cambie, R. C.; Clark, G. R.; Craw, P. A.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1984**, *37*, 1775.
(19) In view of the likeness of bridged biaryls to the helicene, one of us (J.P.R.) has suggested the use of the helicity rule (*P*–*M*) nomenclature instead of the (*R*–*S*) one. Cahn, R. F.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385. See also: Taafrout, M.; Rouessac, F.; Robin, J. P. *Tetrahedron Lett.* **1983**, *24*, 197. For basic studies about the stereochemistry of bisbenzocyclooctadiene, see: Mislow, K.; Wellman, K.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 1342.
(20) Typical procedure: To a stirring suspension of ruthenium(IV) dioxide dihydrate (0.67 mM) in triflic acid (0.8 mL)–triflic anhydride (0.4 mL–methylene chloride (4 mL) at 0 °C was added, under argon, a solution of prestegane B (0.33 mM) in dichloromethane (4 mL) and immediately boron trifluoride etherate (0.2 mL). After 3 h, the suspended solid was removed by simple filtration. Evaporation and flash chromatography afforded pure crystalline **2b**.

a dibenzylbutanolide lignan bearing a phenol in the meta position, it seemed important to us to verify if our oxidative coupling conditions were able to generate potentially cytotoxic steganins as could be formed in vivo by peroxidases in human blood.[21] Curiously, the same conditions applied to this lignan,[22] and its derivative **1f** gave no reaction.[23]

Hitherto, biogenesis of bisbenzocyclooctadiene lignan lactones has been based on the observation of Kende and Schlessinger[24] involving a spiro dienone as intermediate in oxidative coupling of a nonphenolic precursor.[25] In the case of the lignans of *Steganotaenia araliacea*, it is clear that the present results involving an oxidative coupling in the para or ortho position of the phenol function, offer additional insight into the biogenesis of this rare class of antitumor products.[26]

Acknowledgment. We are indebted to the Ligue Française contre le Cancer and the Institut Henri Beaufour, for grants in support of this research, and to Professor Guy Ourisson for helpful discussions. Dr. Matthew Suffness (NCI, NIH) is gratefully acknowledged for his help in our program.

(21) Enzymic oxygen carriers containing transition metals are ubiquitous as natural catalysts in higher plants (laccases, tyrosinase) and other peroxydases such as ceruloplasmin in human plasma. The biological significance of enterolactone remains unknown; however, we have recently found several interesting pharmacological properties including Na^+,K^+ pump activity: Braquet, P.; Senn, N.; Robin, J. P.; Esanu, A.; Godfraind, T.; Garay, R. *Pharm. Res. Commun.* **1986**, 227 and references cited herein.

(22) Readily available by demethylation of monomethyl enterolactone, itself easily obtained as described in our preceding work from *m*-methoxybenzaldehyde. See ref 11.

(23) As found in TLC and ^1H NMR, and, contrary to prestegane B, enterolactone in solution gave an equilibrated mixture of (a) lactonic form and (b) free and chelated hydroxyacid forms. Crystallization of crude reaction mixtures give only pure enterolactone. More desactivation of BF_3 by the phenolic hydroxyl (see ref 6b) and/or the absence of activating methoxyl of each nucleus and/or chelating of the hydroxyl with lactonic carbonyl with opening of the lactone ring are possible explanations.

(24) (a) Kende, A. S.; Liebeskind, L. S.; Kubiak, C.; Eisenberg, R. *J. Am. Chem. Soc.* **1976**, *98*, 6389. (b) Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772.

(25) Spiro dienone has been isolated from *Eupomatia sp.*: Bowden, B. F.; Read, R. W.; Taylor, W. C. *Aust. J. Chem.* **1981**, *34*, 799.

(26) Additionally, an explanation of in vivo formation of (methylenedioxy)phenyls from *o*-methoxyphenol precursors had been recently proposed: Rueffer, M.; Zenk, M. H. *Tetrahedron Lett.* **1985**, *26*, 201.

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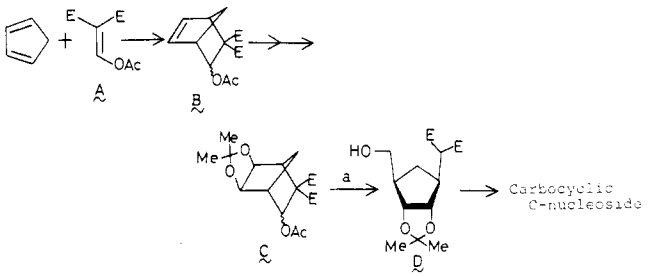
Di-*l*-menthyl (Acetoxymethylene)malonate, a New Chiral Dienophile: Enantioselective Route to Carbocyclic Analogues of C-Nucleoside

Summary: Titanium tetrachloride promoted Diels–Alder reaction of new chiral dienophile, di-*l*-menthyl (acetoxymethylene)malonate, with cyclopentadiene not only proceeds with high diastereofacial selectivity but also provides an efficient enantioselective synthetic route to carbocyclic analogues of C-nucleoside.

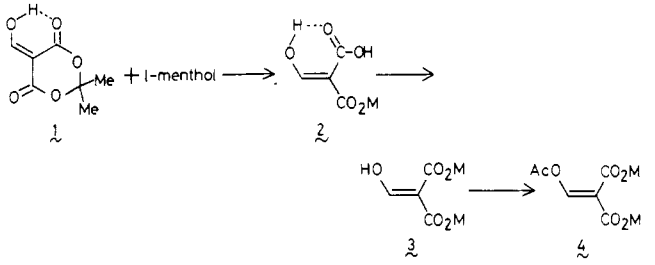
Sir: Recently, we have succeeded in the synthesis of carbocyclic analogues of C-nucleoside via the adduct B obtained by Diels–Alder reaction of dimethyl acetoxymethylenemalonate A with cyclopentadiene.[1] The adduct B was then converted to the acetonide C, whose retrograde aldol C–C bond fission under reductive conditions (a) gave the versatile synthetic building block D with complete stereoselection (Scheme I). Here, we report an successful extension of this methodology to enantioselective synthesis of the compound D by using chiral di-*l*-menthyl acetoxymethylenemalonate (**4**) as a new dienophile.

Scheme I[a,b]



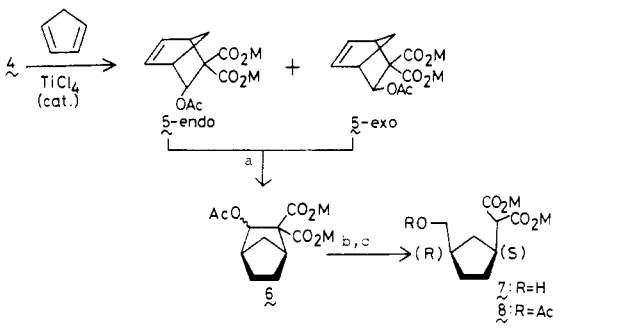
[a] (a) K_2CO_3, $NaBH_4$, MeOH, room temperature. [b] E = CO_2Me.

Scheme II[a]



[a] M = *l*-menthyl.

Scheme III[a,b]



[a] (a) 10% Pd–C, EtOH–ether (2:1); (b) $NaBH_4$, NaOMe–MeOH; (c) $(CH_3CO)_2O$, pyridine, benzene. [b] M = *l*-menthyl.

The synthesis of dienophile **4** was accomplished as follows.[2] Thus, when formyl Meldrum's acid (**1**) was allowed to react with *l*-menthol in benzene at 55 °C, monoester **2** was obtained (Scheme II). *l*-Menthylation of **2** by DCC method (room temperature, 2 h) afforded the diester **3** (mp 58–61 °C) in 46% overall yield from **1**. Usual acetylation (Ac_2O/pyridine, room temperature) of **3** then afforded quantitatively the desired compound **4** as an oil [$[\alpha]^{24}_D$ −43.8° (*c* 4.6, $CHCl_3$); IR ($CHCl_3$) 1790, 1720 cm^{-1};

(1) Katagiri, N.; Haneda, T.; Kaneko, C. *Chem. Pharm. Bull.* **1986**, *34*, 4875. Katagiri, N.; Haneda, T.; Tomizawa, S.; Kaneko, C. *Nucleic Acids Res. Symp. Ser.* **1986**, *17*, 1.

(2) Previously, we have synthesized dimethyl acetoxymethylenemalonate (**A**) via dimethyl methoxymethylenemalonate obtained by the reaction of dimethyl malonate and trimethyl orthoformate.[1] The same procedure could not be applied to the synthesis of **4** from di-*l*-menthyl malonate, because the latter did not react with trimethyl orthoformate under any conditions.

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