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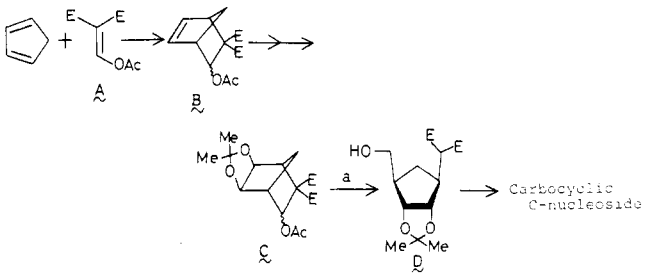
Di-*l*-menthyl (Acetoxymethylene)malonate, a New Chiral Dienophile: Enantioselective Route to Carbocyclic Analogues of C-Nucleoside

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.

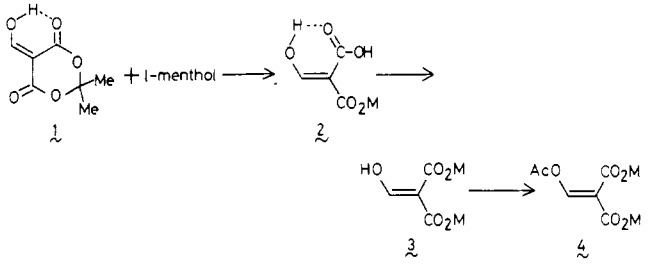
Sir: Recently, we have succeeded in the synthesis of carbocyclic analogues of C-nucleoside via the adduct B obtained by Diels–Alder reaction of dimethyl acetoxymethylenemalonate A with cyclopentadiene.[1] The adduct B was then converted to the acetonide C, whose retrograde aldol C–C bond fission under 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]



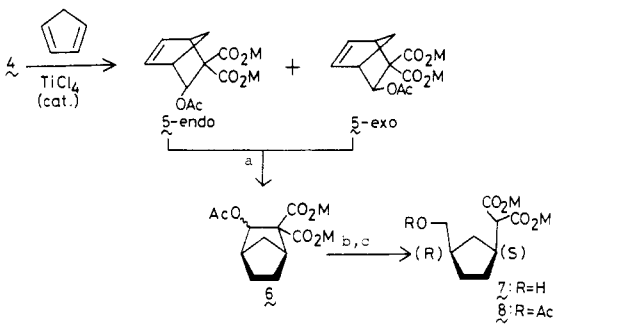
[a] (a) K_2CO_3, $NaBH_4$, MeOH, room temperature. [b] E = CO_2Me.

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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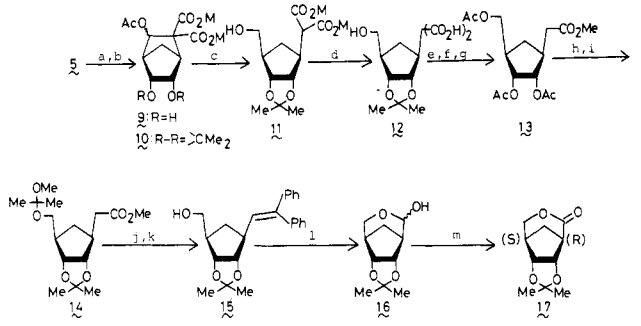
Scheme IV[a,b]



[a] (a) OsO_4, 4-methylmorpholine *N*-oxide (60 wt % solution in water), acetone–ether; (b) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, acetone; (c) $NaBH_4$, NaOMe–MeOH; (d) NaOH, MeOH; (e) CH_3CO_2H, reflux; (f) $(CH_3CO)_2O$–pyridine; (g) CH_2N_2, ether; (h) NH_3–MeOH; (i) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, acetone; (j) PhMgBr, THF; (k) CH_3CO_2H; (l) O_3, CH_2Cl_2, −78 °C; (m) dipyridine–chromium(VI) oxide, CH_2Cl_2. [b] M = *l*-menthyl.

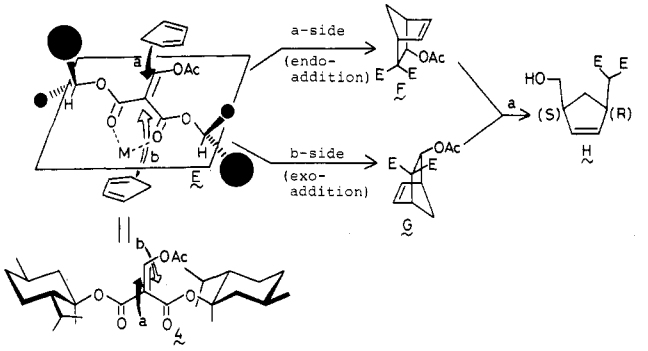
^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3 H, Me), 4.47–5.15 (m, 2 H, menthyl 1–H X 2), 8.43 (s, 1 H, olefinic H)].

Although **4** did not react with cyclopentadiene in toluene at 80 °C, addition of 0.1 molar equiv (to **4**) of $TiCl_4$ in the reaction mixture gave the 4 + 2 adduct **5** in 83% yield even at −78 °C (Scheme III). The adduct was found to be a mixture of endo and exo isomers (ca. 3/1) as judged from ^{1}H NMR spectroscopy. The mixture was then hydrogenated over Pd/C (methanol, 1 atm, room temperature) to give the dihydro derivative **6** again as a mixture of both isomers. Treatment of **6** by the retrograde aldol C–C bond fission reaction under reductive conditions (NaOMe/$NaBH_4$/MeOH, room temperature)[3] afforded the ring fission product **7** in 81% yield. Examination of the acetylated product **8** (mp 49–51 °C) by ^{1}H NMR spectroscopy using shift reagent [Eu(fod), tris[[(heptafluoro)butanoyl]pivaloylmethanato]europium] revealed its enantiomeric excess as >90%. The enantiomeric excess of the reaction was reduced to 71% when the addition was carried out at −15 °C.

The absolute configuration of the adduct **5** was determined by its transformation to the lactone **17** (Scheme IV), whose absolute structure was determined already.[4] Thus, **5** was transformed to chiral carbocyclic C-nucleoside precursor **11** [$[\alpha]^{27}_D$ −39.7° (*c* 2.6, $CHCl_3$)] by a route essentially the same as the conversion of B to D (cf. Scheme I).[1] The diacid **12** obtained by basic hydrolysis was refluxed in acetic acid to give the monoacid. After acetylation followed by methylation (CH_2N_2 in ether), the ester **13** was treated with ammonia in methanol to give a triol, which was allowed to react with 2,2-dimethoxypropane in acetone with trace of TsOH (room temperature) to give the acetonide **14** [$[\alpha]^{22}_D$ −6.9° (*c* 1.2, $CHCl_3$)]. Grignard reaction (PhMgBr–THF) followed by treatment with acetic acid then afforded **15**, which by ozonolysis followed by Collins oxidation afforded the bicyclic compound **17** [mp 141–143 °C; $[\alpha]^{26}_D$ +41° (*c* 0.19, $CHCl_3$); lit. mp 140–141.5 °C, $[\alpha]^{25}_D$ +44.4° (*c* 1.0, $CHCl_3$)].[4]

In our case only a catalytic amount of $TiCl_4$ is needed, whereas for the corresponding fumarate series the amount of this reagent or other Lewis acid catalysts was 1 or more molar equiv to dienophiles.[5] This shows that $TiCl_4$ does chelate with both carbonyl groups at the same time (E in Scheme V)[6] and this chelated species is the only dienophile in our reaction.[7] In order to account for remarkable diastereoselectivity in the addition step, we must assume that the C_2–C_3 moiety of cyclopentadiene is more bulky than the C_5 moiety. Then, one would expect a predominant formation of either the endo or exo isomer (F from a-side attack or **G** from b-side attack), and both of them finally afford a single enantiomer (H) through the C–C bond cleavage reaction (a).

Scheme V[a,b]



[a] (a) See Scheme I. [b] M = $TiCl_4$; E = CO_2(*l*-menthyl).

We are currently investigating the synthesis of some carbocyclic analogues of C-nucleoside using the adduct **5**[8] as well as use of the related dimenthyl methylenemalonates as the dienophiles in asymmetric Diels–Alder reactions.[9]

Acknowledgment. This research was supported in part by Grant-in-Aids from the Research Foundation for Pharmaceutical Sciences, Japan.

(3) The C–C bond fission reactions under reductive conditions of **6** and **10** can be accomplished essentially in the same manner as in the racemic series C → D. The only difference is the use of sodium methoxide instead of potassium carbonate, since the C–C bond fission reaction by use of the latter as an base proceeded much slower due to steric hindrance of the menthyl groups.

(4) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4044.

(5) (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333. (b) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1984**, *106*, 3806. (c) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507.

(6) Poll, J.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112.

(7) Very recently, Houk and co-workers have reported the conformational studies of chiral acrylates–Lewis acid complexes in connection with their asymmetric Diels–Alder reactions: Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(8) The carbocyclic analogue of oxazinomycin recently synthesized in our laboratory exhibits interesting biological activity even in its racemic form: Katagiri, N.; Tomura, M.; Haneda, T.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1422.

(9) We have recently found that di-*l*-menthyl methylenemalonate also reacts with cyclopentadiene in the presence of a catalytic amount of $TiCl_4$ at −78 °C to give the Diels–Alder adduct in high diastereomeric excess. This fact shows that the presence of an acetoxy group in **4** does not play a significant role in determining the diastereoselection in the Diels–Alder reaction of **4** with cyclopentadiene.

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Total Synthesis of Pentalenolactone G Methyl Ester

Summary: The total synthesis of pentalenolactone G has been achieved by a general synthetic approach featuring an intramolecular [2 + 2] photocycloaddition as the key tactic.

Sir: The family of humulene-derived natural products produced by *Streptomyces arenae* known as the penta-

