Asymmetric synthesis of podophyllotoxin analogs

JAMES L. CHARLTON,[1] GUY L. PLOURDE, K. KOH, AND ANTHONY S. SECCO
Department of Chemistry, University of Manitoba, Winnipeg, Man., Canada R3T 2N2

Received January 8, 1990

JAMES L. CHARLTON, GUY L. PLOURDE, K. KOH, and ANTHONY S. SECCO. Can. J. Chem. **68**, 2022 (1990).

Two analogs of podophyllotoxin, with the same absolute stereochemistry as the natural product, have been synthesized from the cycloadduct between α-hydroxy-α′-phenyl-*o*-quinodimethane and the fumarate of *S*-methyl lactate. After initial attempts to produce the cycloadduct from photochemically generated α-hydroxy-α′-phenyl-*o*-quinodimethane failed, a study of the thermal generation and reaction of α-hydroxy-*o*-quinodimethane with the fumarate and acrylate of *S*-methyl lactate was made. A comparison was made of the diastereoselectivity of these cycloaddition reactions to those previously reported, in which the *o*-quinodimethane was generated photochemically. The α-hydroxy-*o*-quinodimethane was produced both by the known thermolysis of benzocyclobutenol and by thermolysis of 1-hydroxy-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide. The diastereomeric excess for the cycloaddition reactions was found to be greater than 95% with modest (ca. 55%) isolated yields of the major cycloadducts. Following these model studies, it was found that α-hydroxy-α′-phenyl-*o*-quinodimethane produced thermally from 1-hydroxy-3-phenyl-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide could be added to the fumarate of *S*-methyl lactate with high diastereoselectivity and good yield. The product of this reaction was converted to the podophyllotoxin analogs **7** and **17**.

Key words: *o*-quinodimethanes, asymmetric, Diels–Alder, lactate, podophyllotoxin, lignan.

JAMES L. CHARLTON, GUY L. PLOURDE, K. KOH et ANTHONY S. SECCO. Can. J. Chem. **68**, 2022 (1990).

Utilisant le cycloadduit obtenu par condensation de 1′α-hydroxy-α′-phényl-*o*-quinodiméthane et du fumarate du lactate de *S*-méthyle, on a synthétisé deux analogues de la podophyllotoxine possédant la même stéréochimie que le produit naturel. Il n'a pas été possible de produire le cycloadduit à partir de l'α-hydroxy-α′-phényl-*o*-quinodiméthane obtenu photochimiquement; on a donc utilisé une méthode thermique pour générer 1′α-hydroxy-*o*-quinodiméthane et pour réaliser sa réaction avec le fumarate du lactate de *S*-méthyle. On a effectué une comparaison de la diastéréosélectivité de ces réactions de cycloaddition avec celles rapportées antérieurement, alors que 1′*o*-quinodiméthane avait été généré d'une façon photochimique. L'-α-hydroxy-*o*-quinodiméthane a été obtenu par la thermolyse connue du benzocyclobuténol ainsi que par la thermolyse du 1-hydroxy-1,3-dihydrobenzo[*c*]thiophène-2,2-dioxyde. On a trouvé que l'excès de diastéréomères est plus grand que 95% alors que le rendement en cycloadduits principaux isolés n'est que de 55%. À la suite de ces études modèles, on a trouvé que 1′α-hydroxy-α′-phényl-*o*-quinodiméthane obtenu thermiquement à partir du 1-hydroxy-3-phényl-1,3-dihydrobenzo[*c*]thiophène-2,2-dioxyde peut être additionné au fumarate du lactate de *S*-méthyle avec une excellente diastéréosélectivité et un excellent rendement. Le produit de cette réaction peut être transformé dans les analogues **7** et **17** de la podophyllotoxine.

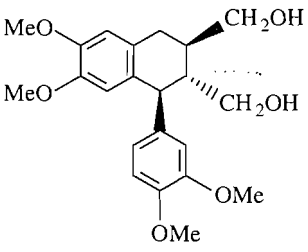
Mots clés : *o*-quinodiméthanes, asymétrique, Diels–Alder, lactate, podophyllotoxine, lignane.

[Traduit par la revue]

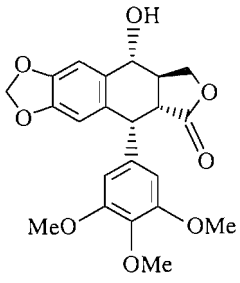
Introduction

The synthesis of aryl tetralin ligans such as dimethyl isolariciresinol or podophyllotoxin requires the stereoselective and asymmetric synthesis of several contiguous chiral centers.

As an approach to these systems, we have been investigating the Diels–Alder reactions of *ortho*-quinodimethanes (*o*-QDMs) (1–4). In our earlier work, we studied the reactions of chiral α-alkoxy-*o*-QDMs with achiral dienophiles, a method that we

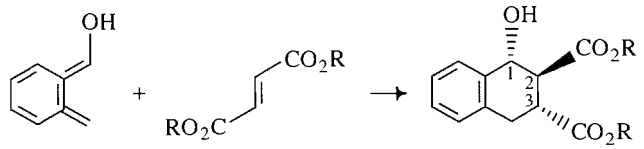


Isolariciresinol dimethyl ether



Podophyllotoxin

eventually used for the synthesis of dimethyl isolariciresinol (3). While these Diels–Alder additions gave good relative stereoselectivity, the absolute stereoselectivity was poor (diastereomeric excess (de) 70%). In addition, the method was not useful for the synthesis of systems having the relative stereochemistry found in podophyllotoxin and compounds of similar



relative stereochemistry. In more recent work, we discovered that the fumarate of *S*-methyl lactate would add to α-hydroxy-*o*-QDM with very high asymmetric induction (de >90%), giving cycloadducts with the same relative stereochemistry as podophyllotoxin at centers 1, 2, and 3 (1, 5).

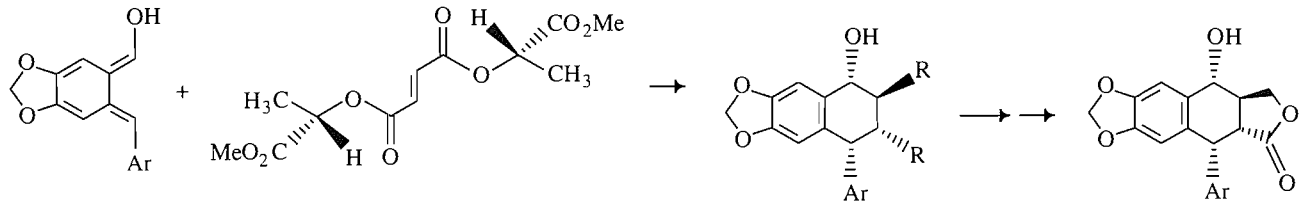
A synthesis of podophyllotoxin itself would require the asymmetric addition of the fumarate of *S*-methyl lactate to an *E*,*E*-α-hydroxy-α′-aryl-*o*-QDM as illustrated (the first asymmetric synthesis of podophyllotoxin has recently been published, ref. 6). There was some doubt about the viability of this approach since earlier work on the cycloaddition of aryl substituted *o*-QDMs with fumarates had shown that the product usually had the 4-aryl and neighboring 3-carboxyl groups *trans* to one another, unlike the desired cycloadduct above (7, 8).

As a model for the proposed podophyllotoxin study we carried out the sequence of reactions shown in Scheme 1 and prepared the optically pure analog **7**, a compound that was previously prepared in racemic form by Macdonald and Durst (9).

Results and discussion

On the basis of the original work of Sammes and co-workers, it was anticipated that the simplest method for the preparation of

[1]Author to whom correspondence may be addressed.



Ar = 3,4,5-trimethoxyphenyl; R = *S*-methyl lactylcarboxy

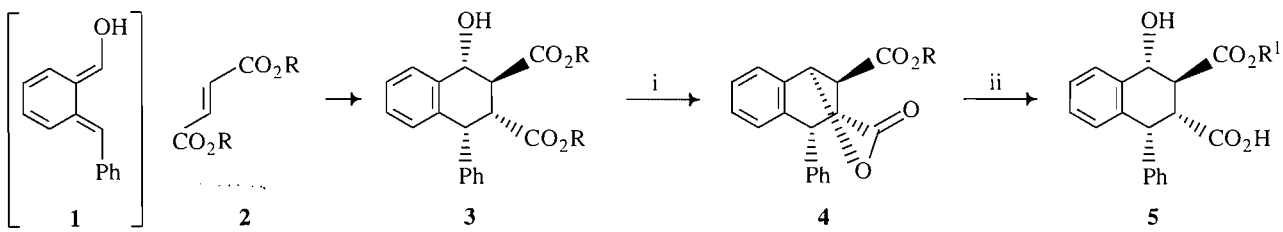
Podophyllotoxin

the *o*-quinodimethane **1** would be the photolysis of *o*-benzylbenzaldehyde (10). Unfortunately, when *o*-benzylbenzaldehyde was irradiated in the presence of the fumarate of *S*-methyl lactate **2** (benzene, 25°C, 450-watt medium pressure Hg lamp, Pyrex filter), no cycloadducts formed after 6 h. The only product detectable in the nmr spectrum was the maleate of *S*-methyl lactate, and the ratio of dilactyl maleate to dilactyl fumarate appeared to be approximately 90:10. Increasing the irradiation time to 30 h did not result in any further change to the reaction mixture. In the hope of increasing the rate of adduct formation, the irradiation was carried out at 110°C in toluene. After 24 h of irradiation at this temperature, only 10% of a possible cycloadduct (appearance of nmr signal near 5 ppm) had formed, in addition to the isomerization of the fumarate.

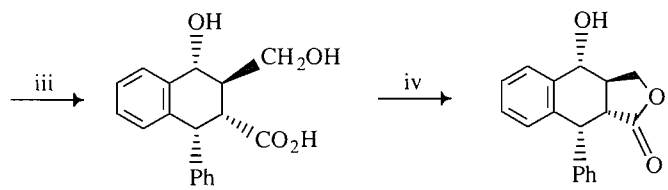
In view of the problems with the photochemical preparation of the *o*-quinodimethane **1**, we turned to methods of thermally generating α-hydroxy-*o*-quinodimethanes. While several methods of thermally preparing *o*-quinodimethanes are known, we were unsure whether the reaction conditions required (solvent, temperature, etc.) would be appropriate for high asymmetric induction in the subsequent addition of the *o*-quinodimethane to the chiral fumarate. To establish suitable experimental conditions, we generated α-hydroxy-*o*-quinodimethane from benzocyclobutenol (**8**, ref. 11) and 1-hydroxy-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide (**9**, ref. 12), and determined the diastereoselectivity of its reaction with both the fumarate and acrylate of *S*-methyl lactate, **2** and **10** (5).

While the thermolysis of benzocyclobutenols to *E*-α-hydroxy-*o*-quinodimethanes was established as a viable procedure by the pioneering work of Sammes and co-workers (13), the corresponding pyrolysis of the benzosulfone **9** to the α-hydroxy-*o*-quinodimethane had not been previously reported. Refluxing benzocyclobutenol **8** in toluene (110°C), in the presence of acrylate **10** (3 equiv.) and a trace of hydroquinone, gave a 73% yield of the cycloadduct **11** (after chromatography, 50:50 ethyl acetate/hexane) (1). A trace of a second isomer **13** could also be detected in the nmr of the crude product (**13**:**11** = 5:95) and, although we never isolated and characterized this adduct, it was suspected that it had the structure **13** because of its large *trans*-H,1,H-2 coupling constant of 9 Hz.

Refluxing benzocyclobutenol (**8**) in toluene in the presence of fumarate **2** (2 equiv.) gave exclusively **12** in 58% yield after chromatography (15% ethyl acetate in hexane) (1). **12** was also the exclusive product (55% isolated yield) when the sulfone **9** was added dropwise (in CH_2Cl_2) to a refluxing solution of fumarate **2** in toluene, showing that hydroxy sulfones such as **9** do thermalize readily to the corresponding α-hydroxy-*o*-quinodimethane. Attempts to prepare cycloadducts with the acrylate **10** using sulfone **9** as a precursor failed completely, with only *o*-methylbenzaldehyde and the starting acrylate being isolated from the reaction. This failure is presumably due to the lower reactivity of the acrylate in the Diels–Alder reaction, and the presence of SO_2 from the thermolysis of the sulfone, which may form sulfurous acid with traces of water and catalyze the tautomerization of the *o*-quinodimethane to *o*-methylbenzaldehyde. The asymmetric induction observed (ca. 95% de) in the reactions of thermally generated α-hydroxy-*o*-quinodimethane with the acrylate and fumarate of *S*-methyl lactate is comparable to that observed at ambient temperature when the *o*-quinodimethane was generated photochemically (1).

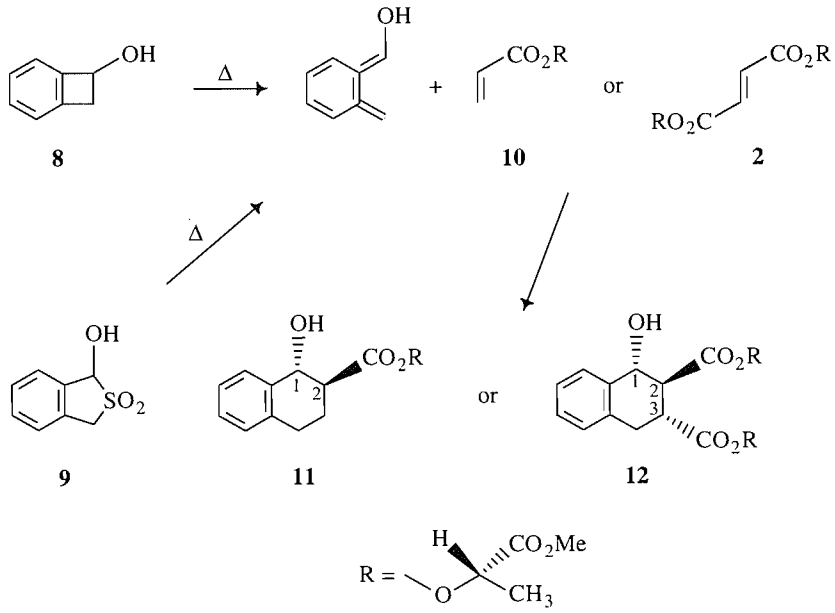


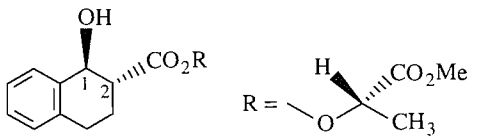
R^1 = -CH(CH_3)CO_2H (S) R = -CH(CH_3)CO_2H (S)



(i) *n*-BuLi, 1 equiv., THF, 10 min at −78 °C, 20 min at 20 °C; (ii) 10% HCl/*t*-BuOH 4:2.5, 3.5 days at 80 °C;
(iii) $LiBHEt_3$, 5.5 equiv., THF, 5 min at 0 °C, 24 h at 20 °C, work-up 10% HCl 24 h at 20 °C;
(iv) DCC, 1 equiv., THF, 24 h at 20 °C.

SCHEME 1

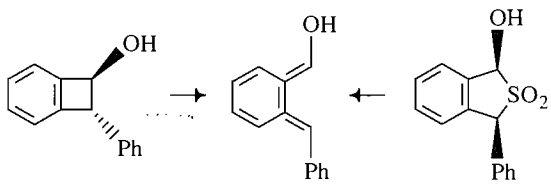




13

Turning our attention once again to Scheme 1, we considered the choice of generating the *o*-quinodimethane **1** from *trans*-1-hydroxy-2-phenylbenzocyclobutenol **14** or from *cis*-1-hydroxy-3-phenylsulfone **15**.

In view of the thermal instability of **14**, and the difficulties that others have had in its preparation (14–16), we decided against the benzocyclobutenol approach. We were pleased to find that slowly adding a methylene chloride solution of the sulfone **15** (17) to a refluxing toluene solution of the fumarate **2** led to a crystalline adduct in 55% yield after chromatography (20% ethyl acetate in hexane). Alternatively, the cycloadduct could be crystallized directly from the reaction mixture in 40% yield.



14 1 15

The nmr of the crude reaction mixture indicated that an isomeric cycloadduct was also present. This adduct (5% yield) was subsequently purified by careful chromatography but, although it was fully characterized, its relative and absolute stereochemistry were not determined.[2]

Although we tentatively assigned structure **3** to the major cycloadduct on the basis of the 9-Hz coupling constant between H-1 and H-2, more absolute proof of its structure was required. Treating the adduct with butyl lithium in THF converted it to the lactone **4**, proving the *cis*-1,3 arrangement of the 1-hydroxyl

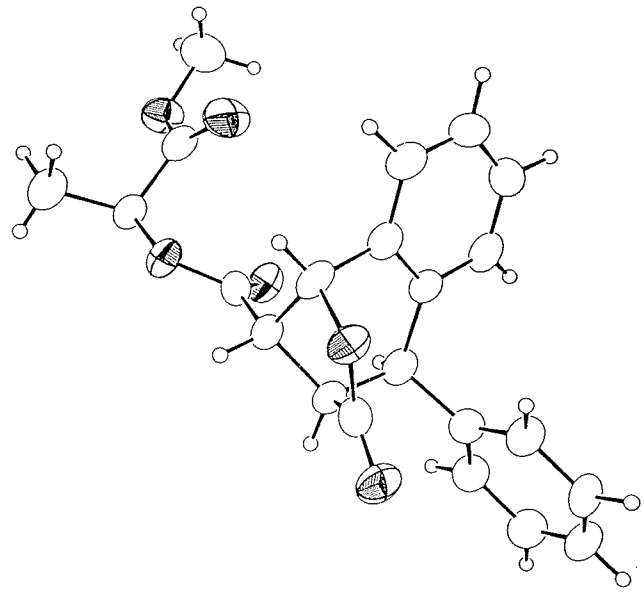


FIG. 1. Diagram of the lactone, **4**; thermal ellipsoids at 50% probability level.

and 3-carboxyl groups in the cycloadduct. In addition, X-ray crystallographic analysis of a crystal of **4** yielded the structure shown in Fig. 1, confirming the relative stereochemistry in **4** and, by inference, the relative stereochemistry in **3**.

Since the absolute stereochemistry of the lactyl group is known (*S*), then the absolute stereochemistries of **3** and **4** can be assigned as shown in Scheme 1.

Several routes from the cycloadduct **3** to the podophyllotoxin analog **7** were considered. Reduction of the 2-ester group in **3** with Super Hydride[3] has precedence in the literature (8), but we were unable to obtain selective reduction in high yield using this procedure. Since conversion of the ester at the 3 position to the acid would protect it during reduction by Super Hydride (18), we attempted to selectively hydrolyze the lactone **4**. This was

[2]The small coupling constant between H-1 and H-2 (3.2 Hz) suggests that this minor isomer has a *cis*-1,2 stereochemistry.

[3]Super Hydride is a registered trademark of Aldrich Chemical Company for lithium triethylborohydride.

TABLE 1. Fractional atomic coordinates (esd's) and equivalent isotropic temperature factors, B_{eq}(Å^2) for the lactone, **4**

Atom	*x*	*y*	*z*	B_{eq}
O(1)	0.0889(2)	−0.7030	−0.3912(2)	1.97(8)
O(2)	0.1617(2)	−0.5199(4)	−0.4865(2)	2.52(9)
O(3)	−0.2667(2)	−0.4864(4)	−0.2841(2)	2.23(9)
O(4)	−0.3634(2)	−0.6764(3)	−0.4132(2)	2.03(8)
O(5)	−0.3238(3)	−0.7955(4)	−0.1894(2)	2.9(1)
O(6)	−0.5382(2)	−0.7015(4)	−0.1933(2)	2.5(1)
C(1)	−0.1339(3)	−0.6008(5)	−0.4034(3)	1.8(1)
C(2)	−0.0229(3)	−0.7183(5)	−0.3332(3)	1.8(1)
C(3)	0.0459(3)	−0.6818(5)	−0.1988(3)	1.7(1)
C(4)	0.0719(3)	−0.7914(5)	−0.1094(3)	2.0(1)
C(5)	0.1363(4)	−0.7551(5)	0.0136(3)	2.4(1)
C(6)	0.1730(4)	−0.6090(5)	0.0470(3)	2.5(1)
C(7)	0.1464(4)	−0.4996(5)	−0.0416(3)	2.1(1)
C(8)	0.0821(3)	−0.5335(4)	−0.1660(3)	1.6(1)
C(9)	0.0436(4)	−0.4107(5)	−0.2619(3)	1.8(1)
C(10)	−0.0268(3)	−0.4730(5)	−0.3950(3)	1.8(1)
C(11)	0.0860(4)	−0.5602(5)	−0.4313(3)	2.1(1)
C(12)	−0.2584(3)	−0.5678(5)	−0.3566(3)	1.8(1)
C(13)	−0.4890(3)	−0.6800(5)	−0.3740(3)	1.9(1)
C(14)	−0.4363(3)	−0.7324(5)	−0.2415(3)	1.9(1)
C(15)	−0.5047(5)	−0.7451(7)	−0.0661(4)	3.1(2)
C(16)	−0.5935(4)	−0.7915(5)	−0.4571(4)	2.6(1)
C(17)	0.1717(4)	−0.3085(5)	−0.2519(3)	1.8(1)
C(18)	0.1501(4)	−0.1536(5)	−0.2611(3)	2.1(1)
C(19)	0.2640(4)	−0.0578(5)	−0.2572(3)	2.5(1)
C(20)	0.3980(4)	−0.1155(5)	−0.2451(3)	2.4(1)
C(21)	0.4230(4)	−0.2681(5)	−0.2345(3)	2.2(1)
C(22)	0.3100(4)	−0.3622(5)	−0.2368(3)	2.0(1)

TABLE 2. Non-hydrogen atom bond lengths (esd's) in Å for the lactone, **4**

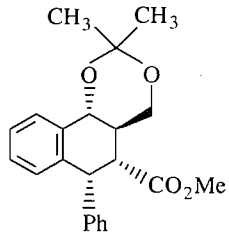
Bond	Length	Bond	Length
O(1)—C(2)	1.477(4)	C(5)—C(6)	1.378(6)
O(1)—C(11)	1.360(4)	C(6)—C(7)	1.380(6)
O(2)—C(11)	1.193(4)	C(7)—C(8)	1.392(5)
O(3)—C(12)	1.194(4)	C(8)—C(9)	1.519(5)
O(4)—C(12)	1.343(4)	C(9)—C(10)	1.558(5)
O(4)—C(13)	1.450(4)	C(9)—C(17)	1.520(5)
O(5)—C(14)	1.191(4)	C(10)—C(11)	1.525(5)
O(6)—C(14)	1.331(4)	C(13)—C(14)	1.517(5)
O(6)—C(15)	1.452(5)	C(13)—C(16)	1.509(5)
C(1)—C(2)	1.525(5)	C(17)—C(18)	1.404(5)
C(1)—C(10)	1.531(5)	C(17)—C(22)	1.382(5)
C(1)—C(12)	1.510(5)	C(18)—C(19)	1.393(5)
C(2)—C(3)	1.502(5)	C(19)—C(20)	1.365(6)
C(3)—C(4)	1.388(5)	C(20)—C(21)	1.388(5)
C(3)—C(8)	1.395(5)	C(21)—C(22)	1.381(5)
C(4)—C(5)	1.383(5)		

accomplished in aqueous, acidic *tert*-butyl alcohol (which also hydrolyzes the carboxymethyl group in the lactyl side chain), to give **5**. Selective reduction of the lactyl ester in **5** with Super Hydride gave the acid-diol **6**. Both **5** and **6** were extremely polar and could not be purified by chromatography on silica gel and we were also unable to crystallize these compounds. The acid-diol **6** was converted to its methyl ester/acetonide **16**, which we were able to purify by chromatography and fully characterize.

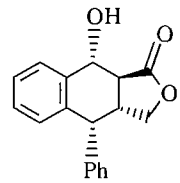
When **6** was treated with dicyclohexylcarbodiimide (DCC) in THF, it was converted to the lactone **7** (isolated by chromatography on silica gel, 30% EtOAc/hexane, and recrystallization from CH_2Cl_2/hexane), whose nmr was identical to that of the racemic compound published earlier by Macdonald and Durst (9).

The complete reaction sequence shown in Scheme 1 can be carried out with purification of only the cycloadduct **3** (chromatography on silica gel) and the final product **7** (chromatography on silica gel), to give an overall yield of 16% based on the hydroxy sulfone **15**.

In the course of our investigation we also attempted to reduce the lactone **4** with Super Hydride.[3] On work-up in dilute acid we obtained the optically pure lactone **17** in 70% yield as a crystalline solid. The high yield of this procedure suggests that it may be applicable to preparation of other pericarbonyl lignans.



16



17

The work described here is being extended to the asymmetric synthesis of natural lignans and other lignan analogs.

Experimental

The ^{1}H nmr spectra were recorded on a Bruker AM-300 instrument using tetramethylsilane as internal standard. The ir spectra were recorded on a Perkin Elmer 881 spectrometer. Merck Kieselgel 60 was used for all chromatography. Exact Mass/mass spectra were obtained on an Analytical VG 7070E-HF instrument. Melting points were measured on a hot stage instrument and are uncorrected. Optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument.

1-Hydroxy-3-phenyl-1,3-dihydrobenzo[c]*thiophene-2,2-dioxide, **15***

15 was prepared, using the procedure described for **9** (17), but without base extraction of the final product. To a solution of *o*-benzylbenzaldehyde (4.35 g, 22.2 mmol) in benzene (100 mL) was added a solution of sulfur dioxide (18 g) in benzene (15 mL). The volume of the solution was adjusted to fill the reaction vessel (~300 mL); the solution was flushed with nitrogen and irradiated for 20 h using a 450-watt Hanovia medium pressure mercury lamp located in a water-cooled, Pyrex probe immersed in the solution. The probe was cleaned every five hours. The solution was evaporated and the residue triturated with carbon tetrachloride to afford a yellowish solid (4.0 g, 69%) corresponding to the *cis*-hydroxy sulfone; ^{1}H nmr ($CDCl_3$) δ: 3.1 (br s, 1H, OH), 5.3 (s, 1H, H-2), 5.67 (s, 1H, H-1), 7.1–7.7 (m, 9H, aromatics), identical to that previously reported (17).

(−)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)*-methyl lactate, **11***

To a solution of benzocyclobutenol **8** (32.2 mg, 0.268 mmol) in toluene (7 mL) was added (*S*)-methyl lactyl acrylate (127 mg, 0.804 mmol, 3 equiv.) and hydroquinone (2 mg). The solution was refluxed for 6 h, cooled, and the solvent evaporated. Chromatography on silica gel using 50% ethyl acetate/hexane as eluant afforded a colourless solid (54.4 mg, 73%, see ref. 1 for properties).

(−)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (S)*-methyl lactate, **12***

Method A: From benzocyclobutenol 8

To a solution of benzocyclobutenol **8** (28 mg, 0.23 mmol) in toluene (5 mL) was added (*S*)-methyl lactyl fumarate (221 mg, 0.77 mmol, 3.3 equiv.) and 4Å molecular sieves (20 mg). The solution was refluxed for

4 h, cooled, and the solvent evaporated. Chromatography on silica gel using 15% ethyl acetate/hexane as eluant afforded a colourless solid (55 mg, 58%; see ref. 1 for properties).

Method B: From benzosulfone ***9***

To a refluxing solution of (*S*)-methyl lactyl fumarate (292 mg, 1.01 mmol, 1.5 equiv.) in toluene (5 mL) containing zinc oxide powder (50 mg) was slowly added a methylene chloride solution (5 mL) of hydroxy sulfone **9** (124 mg, 0.67 mmol). After addition of the methylene chloride solution, the mixture was refluxed for another 20 min, cooled, eluted through a short silica gel column with ethyl acetate, and evaporated. The residual oil was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to afford a colourless solid (152 mg, 55%). Recrystallization from hexane gave colourless plates (see ref. 1 for properties).

(−)-1-Hydroxy-4-phenyl-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (S)*-methyl lactate,* ***3***

To a refluxing solution of (*S*)-methyl lactyl fumarate **2** (973 mg, 3.38 mmol, 1.5 equiv.) in toluene (20 mL) containing zine oxide powder (200 mg) was slowly added, over a period of 1 h, a solution of hydroxy sulfone **15** (580 mg, 2.23 mmol) in methylene chloride (25 mL). The solution was then refluxed for 20 min, filtered through a short silica gel column using ethyl acetate as eluant, and evaporated to give a yellow oil (2 isomers, 90:10 ratio from ^{1}H nmr of crude). The crude product was purified by chromatography using 15% ethyl acetate/hexane as eluant to afford a colourless oily material for each isomer: 582.9 mg, 54%, major; 60.6 mg, 5.6%, minor; 643.5 mg, 60%, total yield. Recrystallization of the major isomer from isopropyl alcohol afforded colourless needles. The major isomer could also be obtained in 40% yield by recrystallization of the crude product from isopropyl alcohol. The minor isomer could not be crystallized.

Major isomer, ***3***: mp 142–143°C; $[\alpha]_D$ −215° (*c* 0.2, $CHCl_3$); ir (CH_2Cl_2): 3476 (OH), 1742 (CO) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.09 (d, 3H, *J* = 7.0, CH_3), 1.53 (d, 3H, *J* = 7.2, CH_3), 3.33 (dd, 1H, *J* = 9.5, 12.5, H-2), 3.55 (dd, 1H, *J* = 5.7, 12.5, H-3), 3.73 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.69 (d, 1H, *J* = 5.7, H-4), 4.91 (q, 1H, *J* = 7.0, CH), 4.98 (d, 1H, *J* = 9.5, H-1), 5.32 (q, 1H, *J* = 7.2, CH), 7.13 (m, 8H, aromatics), 7.82 (d, 1H, *J* = 7.4, H-8); ms, *m/e* (rel. %): 484 (<0.1), 362 (1.6), 335 (17), 334 (75), 249 (13), 248 (16), 247 (9), 232 (20), 231 (100). Exact Mass calcd. for $C_{26}H_{28}O_9$: 484.1733; found: 484.1697. Anal. calcd. for $C_{26}H_{28}O_9$: C 64.46, H 5.83; found: C 64.29, H 5.97.

Minor isomer: $[\alpha]_D$ +50° (*c* 0.18, $CHCl_3$); ir (CH_2Cl_2): 3477 (OH), 1737 (CO) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.32 (d, 3H, *J* = 6.9, CH_3), 1.59 (d, 3H, *J* = 7.2, CH_3), 3.41 (dd, 1H, *J* = 3.1, 11.9, H-2), 3.60 (s, 3H, OCH_3), 3.71 (overlapping dd, 1H, *J* = 11.5, H-3), 3.81 (s, 3H, OCH_3), 4.02 (d, 1H, *J* = 4.0, OH), 4.17 (d, 1H, *J* = 11.1, H-4), 4.97 (q, 1H, *J* = 6.9, CH), 5.27 (q, 1H, *J* = 7.2, CH), 5.44 (overlapping dd, 1H, *J* = 3.5, H-1), 6.76 (d, 1H, *J* = 7.8, H-5), 7.12–7.35 (m, 7H, aromatics), 7.43 (d, 1H, *J* = 7.8, H-8); ms, *m/e* (rel. %): 484 (0.1), 334 (18), 250 (19), 249 (16), 248 (17), 247 (12), 232 (22), 231 (100).

Lactone, ***4***

To a solution of hydroxycycloadduct **3** (448.8 mg, 0.93 mmol) in dry tetrahydrofuran (20 mL) was added, at −78°C under nitrogen, *n*-butyllithium in hexanes (2.5 M, 0.37 mL, 0.93 mmol). The solution was stirred at −78°C for 15 min, then at room temperature for 0.5 h. Aqueous ammonium chloride (5%, 30 mL) was added, and the solution stirred for 15 min, extracted with methylene chloride, dried ($MgSO_4$), and evaporated to give an oil (316.2 mg, 90%, >90% pure by ^{1}H nmr). Chromatography on silica gel using 15% ethyl acetate/hexane as eluant afforded a colourless solid (185.4 mg, 51%). Recrystallization from hexane/methylene chloride gave colourless flakes. Crystals were suitable for X-ray analysis; mp 135–136°C; $[\alpha]_D$ −39.3° (*c* 0.18, $CHCl_3$); ir (CH_2Cl_2): 1788 (CO, lactone), 1748 (CO, ester) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.42 (d, 3H, *J* = 7.0, CH_3), 3.35 (td, 1H, *J* = 0.8, 4.9, H-3), 3.51 (s, 3H, OCH_3), 3.94 (t, 1H, *J* = 5.1, H-2), 4.95 (d, 1H, *J* = 4.9, H-4), 5.00 (q, 1H, *J* = 7.0, CH), 5.52 (d, 1H, *J* = 5.1, H-1), 7.0–7.4 (m, 9H, aromatics); ms, *m/e* (rel. %): 380 (0.4), 362 (4.3), 334 (32), 276 (16), 248 (32), 231 (79), 220 (22), 205 (68), 204 (100), 192 (39). Exact Mass calcd. for $C_{22}H_{20}O_6$: 380.1259; found: 380.1254.

Hydroxy diacid, ***5***

To a solution of (*S*)-lactyl lactone **4** (57.6 mg, 0.15 mmol) in *tert*-butyl alcohol (7 mL) was added aqueous HCl (10%, 15 mL). The solution was heated for 3 days using a sand bath maintained at 80°C. Aqueous sodium bicarbonate (5%) was then slowly added until the solution was basic. The solution was extracted with methylene chloride, the aqueous portion reacidified (10% HCl), extracted with ethyl acetate, and dried ($MgSO_4$), and the solvent evaporated to give a colourless solid (42.2 mg, 72%). The product (~90% pure, ^{1}H nmr) could not be recrystallized or chromatographed on silica and was therefore used without further purification; mp 122–130°C; ^{1}H nmr ($CDCl_3$) δ: 1.54 (d, *J* = 7.1, CH_3), 3.24 (dd, *J* = 9.8, 12.4, H-2), 3.54 (dd, *J* = 5.6, 12.4, H-3), 4.67 (d, *J* = 5.4, H-4), 4.98 (d, *J* = 9.8, H-1), 5.31 (q, *J* = 7.1, CH), 6.95–7.33 (m, aromatics), 7.74 (d, *J* = 7.8, H-8), obtained from crude product.

The dimethyl ester of **5** was obtained by treating the crude diacid **5** with diazomethane followed by chromatography (15% ethyl acetate/hexane); ^{1}H nmr ($CDCl_3$) δ: 1.54 (d, 3H, *J* = 7.2, CH_3), 3.28 (dd, 1H, *J* = 9.7, 12.4, H-2), 3.52 (dd, 1H, *J* = 5.8, 12.4, H-3), 3.58 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.68 (d, 1H, *J* = 5.8, H-4), 4.73 (d, 1H, *J* = 3.4, OH), 4.97 (dd, 1H, *J* = 3.1, 9.7, H-1), 5.28 (q, 1H, *J* = 7.2, CH), 6.90–7.35 (m, 8H, aromatics), 7.81 (d, 1H, *J* = 7.9, H-8); ms, *m/e* (rel %): M^+ not observed, 394 (1.1), 334 (29.9), 263 (36), 262 (78.2), 249 (10.1), 248 (10.5), 247 (9.9), 232 (20.2), 231 (100).

Dihydroxy acid, ***6***

To a solution of crude hydroxy diacid **5** (77.5 mg, 0.2 mmol) in dry tetrahydrofuran (40 mL) was added, at 0°C under nitrogen, lithium triethylborohydride in tetrahydrofuran (1 M, 1.3 mL, 1.3 mmol, 6.5 equiv.). The solution was stirred at 0°C for 5 min, then at room temperature for 20 h. Dilute aqueous HCl (10%) was added, and the solution stirred for 1.5 h, saturated with NaCl, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to give a brownish oily material (59.3 mg, 98%). The product (~80% pure, ^{1}H nmr) could not be crystallized or chromatographed on silica and was therefore used without further purification; ir (CH_2Cl_2): 3695 (OH), 1744 (CO) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.53 (m, H-2), 3.06 (dd, *J* = 6.3, 12.1, H-3), 4.35 (dd, *J* = 4.6, 10.7, H-11), 4.62 (d, *J* = 6.3, H-4), 4.86 (d, *J* = 10.1, H-1), 6.85–7.31 (m, aromatics), 7.75 (d, *J* = 7.7, H-8), H-11′ was not observed. Data obtained from crude product.

Methyl ester of dihydroxy acid ***6***

The methyl ester of **6** was obtained by treating the dihydroxy acid with excess diazomethane in diethyl ether and evaporation of the solvent. Purification by chromatography on silica gel was not possible; ^{1}H nmr ($CDCl_3$) δ: 2.59 (m, H-2), 3.05 (dd, *J* = 6.5, 12.1, H-3), 3.49 (s, OCH_3), 4.31 (dd, *J* = 4.5, 10.6, H-11), 4.59 (d, *J* = 6.5, H-4), 4.85 (d, *J* = 10.2, H-1), 6.88–7.32 (m, aromatics), 7.73 (d, *J* = 7.7, H-8), obtained from crude product.

Acetonide, ***16***

This compound was prepared according to a procedure previously reported (19). To a solution of crude dihydroxy ester (see above, 64.8 mg, 0.21 mmol) in 2,2-dimethoxypropane (5 mL) was added *p*-toluenesulfonic acid (trace). The solution was stirred at room temperature overnight. Ethyl acetate was added, the organic solution washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$), and the solvent evaporated to give a semicrystalline product (44.9 mg, 61%). Chromatography on silica gel using 15% ethyl acetate/hexane as eluant gave a colorless oil that could not be crystallized; $[\alpha]_D$ −179.4° (*c* 0.36, $CHCl_3$); ir (CH_2Cl_2): 1742 (CO) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.56 (s, 3H, CH_3), 1.60 (s, 3H, OCH_3), 2.50 (m, 1H, H-2), 3.02 (dd, 1H, *J* = 6.7, 12.3, H-3), 3.40 (s, 3H, CH_3), 3.68 (t, 1H, *J* = 10.9, H-11), 4.14 (dd, 1H, *J* = 4.3, 11.1, H-11′), 4.57 (d, 1H, *J* = 6.7, H-4), 4.79 (d, 1H, *J* = 10.4, H-1), 6.87–7.26 (m, 8H, aromatics), 7.56 (d, 1H, *J* = 7.8, H-8); ms, *m/e* (rel. %): 352 (2.1), 337 (12), 277 (73), 217 (100), 205

(42), 195 (32). Exact Mass calcd. for $C_{22}H_{24}O_4$: 352.1674; found: 352.1671.

Podophyllotoxin analog, 7

The hydroxycycloadduct **3** (532.5 mg, 1.1 mmol) was treated with *n*-BuLi to give the crude lactone **4**. The lactone **4** (445 mg) was then hydrolysed and the residual hydroxy diacid **5** (287.2 mg) was reduced with Super Hydride ($LiBHEt_3$, ref. 14). No purification was performed for any of these first three steps. To a solution of this crude dihydroxy acid **6** (187 mg) in dry tetrahydrofuran (15 mL) was added dicyclohexylcarbodiimide (DCC, 145 mg, 0.7 mmol) in tetrahydrofuran (1 mL). The solution was stirred at room temperature for 24 h and worked up according to literature procedure (4),[2] with addition of water and acetic acid followed by evaporation of the solvent to give a semicrystalline material (241 mg). Purification by trituration with methylene chloride followed by chromatography on silica gel using 25% ethyl acetate/hexane as eluant gave a colourless solid (92.1 mg, 30% from **3**, 16.5% overall from **15**). Recrystallization from hexane/methylene chloride afforded colourless plates; mp 225–227°C (226–227°C for racemic material (9)); $[\alpha]_D$ −151° (*c* 0.12, $CHCl_3$); ir (CH_2Cl_2): 3320 (OH), 1777 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.18 (d, 1H, J = 7.7, OH), 2.87 (m, 2H, H-2, H-3), 4.11 (br t, 1H, J = 9.5, H-11), 4.61 (dd, 1H, J = 6.6, 8.8, H-11′), 4.78 (d, 1H, J = 4.3, H-4), 4.89 (br t, 1H, J = 8.5, H-1), 7.05–7.39 (m, 8H, aromatics), 7.70 (d, 1H, J = 7.8, H-8); ms, *m/e* (rel. %): 280 (51), 262 (35), 218 (45), 217 (54), 119 (53), 117 (100). Exact Mass calcd. for $C_{18}H_{16}O_3$: 280.1099; found: 280.1104.

Pericarbonyl lactone, 17

To a solution of (*S*)-lactyl lactone **4** (228.3 mg, 0.60 mmol) in dry tetrahydrofuran (25 mL) was added, at 0°C under nitrogen, lithium triethylborohydride in tetrahydrofuran (1 M, 1.8 mL, 1.8 mmol, 3 equiv.). The solution was stirred at 0°C for 10 min, then at room temperature for 5 h. Dilute aqueous HCl (10%, 20 mL) was added and the solution was stirred overnight. The solution was diluted with water, extracted with methylene chloride, dried ($MgSO_4$), and evaporated to give a white solid (119.8 mg, 71%). Recrystallization from carbon tetrachloride afforded colourless needles; mp 162–164°C; $[\alpha]_D$ −75.6° (*c* 0.18, $CHCl_3$); ir (CH_2Cl_2): 3577 (OH), 1776 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.74 (dd, 1H, J = 9.9, 14.5, H-2), 2.91–3.03 (m, 1H, H-3), 3.35 (br s, 1H, OH), 3.56 (dd, 1H, J = 8.6, 11.1, H-11), 4.43 (dd, 1H, J = 7.0, 8.6, H-11′), 4.51 (d, 1H, J = 5.7, H-4), 5.07 (d, 1H, J = 9.9, H-1), 6.91–7.80 (m, 9H, aromatics); ms, *m/e* (rel. %): 280 (30), 217 (8), 202 (5), 195 (6), 178 (7), 165 (11), 118 (10), 117 (100). Exact Mass calcd. for $C_{18}H_{16}O_3$: 280.1099, found: 280.1076.

X-ray analysis

Crystal data:

$C_{22}H_{19}O_6$ fw = 379.39

Monoclinic, $P2_1$, a = 9.745 (3), b = 8.974 (4), c = 11.633 (3) Å, β = 110.72 (2)°, V = 951.4 (6) $Å^3$, Z = 2, ρ_c = 1.324 g cm^{-3}, μ = 7.61 cm^{-1}, $F(000)$ = 398 (−150°C; CuKα, λ = 1.54178 Å). Data were collected using a crystal of the lactone **4** measuring 0.25 × 0.25 × 0.10 mm on a Rigaku AFC5R diffractometer with an ω–2θ scan type. 1298 unique reflections were measured within the region bounded by h, k, $\pm l$. Data were corrected for Lorentz and polarization effects yielding 1260 observed reflections with $I > 3\sigma(I)$. The structure was solved by direct methods and refined by full-matrix least-squares techniques minimizing the function $\Sigma w(|F_o| - |F_c|)^2$, where $w = 4F_o^2\sigma^{-2}(F_o^2)$. All non-H atoms were corrected for anomalous scattering and an extinction correction ($g = 0.26 \times 10^{-4}$) was applied. Final agreement factors, $R = \Sigma||F_o| - |F_c||\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/|\Sigma wF_o^2]^{1/2}$ were 0.030 and 0.042, respectively, for the 1260 observed data. The goodness of fit was 1.50 on the last cycle of refinement, which showed a maximum Δ/σ of 0.02. The final difference map indicated electron density fluctuations of −0.13 to 0.42 e $Å^{-3}$. Positional and isotropic thermal parameters are given in Table 1 for all non-H atoms; bond distances involving non-H atoms are listed in Table 2. H atom coordinates, complete lists of bond lengths and angles, temperature factors, and structure factors have been deposited as supplementary material.[4]

Acknowledgements

We would like to acknoweldge the financial assistance of the Natural Sciences and Engineering Research Council of Canada. We would also like to thank Molecular Structure Corporation for assistance in X-ray structure analysis.

1. J. L. CHARLTON, G. L. PLOURDE, K. KOH, and A. S. SECCO. Can. J. Chem. **67**, 574 (1989).
2. J. L. CHARLTON, G. L. PLOURDE, and G. H. PENNER. Can. J. Chem. **67**, 1010 (1989).
3. J. L. CHARLTON and M. M. ALAUDDIN. J. Org. Chem. **64**, 793 (1986).
4. J. L. CHARLTON. Can. J. Chem. **64**, 720 (1986).
5. J. L. CHARLTON, K. KOH, and G. L. PLOURDE. Tetrahedron Lett. **30**, 3279 (1989).
6. R. C. ANDREWS, S. J. TEAGUE, and A. I. MEYERS. J. Am. Chem. Soc. **110**, 7854 (1988).
7. J. L. CHARLTON, M. M. ALAUDDIN, and G. H. PENNER. Can. J. Chem. **64**, 793 (1986).
8. M. B. GLINSKI and T. DURST. Can. J. Chem. **61**, 573 (1982).
9. D. I. MACDONALD and T. DURST. J. Org. Chem. **53**, 3663 (1988).
10. B. J. ARNOLD, S. M. MELLOWS, P. G. SAMMES, and T. W. WALLACE. J. Chem. Soc. Perkins Trans. **1**, 401 (1974).
11. W. A. BUBB and S. STEINHELL. Aust. J. Chem. **29**, 1685 (1976).
12. J. L. CHARLTON and T. DURST. Tetrahedron Lett. **25**, 2663 (1984).
13. B. J. ARNOLD and P. G. SAMMES. J. Chem. Soc. Chem. Commun. 30 (1972); J. Chem. Soc. Chem. Commun. 1034 (1972); B. J. ARNOLD, S. M. MELLOWS, and P. G. SAMMES. J. Chem. Soc. Perkin Trans. 1, 1266 (1973); B. J. ARNOLD, P. G. SAMMES, and T. W. WALLACE. J. Chem. Soc. Perkin Trans. 1. 409 (1974); J. Chem. Soc. Perkin Trans. 1, 415 (1974).
14. M. E. JUNG, P. Y-S. LAM, M. M. MANSURI, and L. M. SPELTZ. J. Org. Chem. **50**, 1087 (1985).
15. M. E. JUNG and G. T. LOWEN. Tetrahedron Lett. **27**, 5319 (1986).
16. D. I. MACDONALD and T. DURST. Tetrahedron Lett. **27**, 2235 (1986).
17. T. DURST, E. C. KOZMA, and J. L. CHARLTON. J. Org. Chem. **50**, 4829 (1985).
18. S. TAKANO, S. OTAKI, and K. OGASAWARA. J. Chem. Soc. Chem Commun. 485 (1985).
19. D. RAJAPAKSA and R. RODRIGO. J. Am. Chem. Soc. **103**, 6208 (1981).

[4]Tables of supplementary data may be purchased from the Depository of Unpublished Data. CISTI, National Research Council of Canada, Ottawa, Ont., Canada, K1A 0S2.