The Role of Dianion Coupling in the Synthesis of Dibenzylbutane Lignans

John L. Belletire, Douglas F. Fry, and Susan L. Fremont

J. Nat. Prod., **1992**, 55 (2), 184-193• DOI:
10.1021/np50080a006 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 55, No. 2, pp. 184-193, February 1992

THE ROLE OF DIANION COUPLING IN THE SYNTHESIS OF DIBENZYLBUTANE LIGNANS

JOHN L. BELLETIRE,* DOUGLAS F. FRY, and SUSAN L. FREMONT

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221-0172

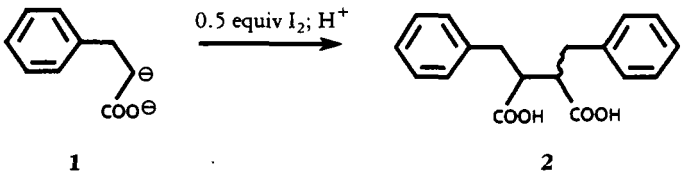
ABSTRACT.—Dianion coupling reactions have been used to prepare structurally related lignan natural products in racemic form. A readily available α-iodocarboxylic acid **10** has been employed in separate sequences to afford the tetrahydrofuran lignan burseran [**6**] and the butyrolactone lignan deoxypodorhizon [**7**]. The key strategy for both burseran and deoxypodorhizon involved reaction of the appropriate dianion with an α-iodo carboxylate salt **13**. Equilibration under acid or base was employed to create the trans stereochemistry of the substituted benzyl side chains of both burseran and deoxypodorhizon. To achieve proper dianion reactivity and to avoid side reactions in the synthetic sequence to deoxypodorhizon, it was necessary to develop the chemistry of acylsulfonamide dianions. As a further structure proof, our synthetic deoxypodorhizon was also utilized as a substrate in a successful sequence to isostegane [**8**], a known relay intermediate to the antineoplastic prototype steganacin [**9**].

Dianions (1), either by reaction with electrophiles (2) or via controlled oxidation (3), are mechanistically attractive (4) intermediates for carbon-carbon bond formation (5). From the perspective of synthetic utility, all carbon-carbon bond-making reactions of dianions can be termed "dianion coupling" and further subclassified according to whether or not these variants have similar or different groups attached to the coupling carbons.

Although it is useful for the construction of both symmetrical and unsymmetrical fatty acid dimers (6), the predominant synthetic application of dianion coupling chemistry has been to a single class of natural products, the lignans. Lignans are characterized by two phenylpropane moieties joined at the central carbon atom of the propyl side chain. Successful coupling of phenylpropionic acid dianion [**1**] yields succinic acid derivative **2**, a molecule possessing the overall lignan skeleton (7) (Scheme 1). Three major classes of lignans (dibenzylbutanes, phenyltetralins, and the dibenzocyclooctanes) are isolable from natural sources. Lignan biosynthesis is conjectured to proceed by a radical oxidative dimerization (8). The variety of possible oxidative functionalizations of the above classes during plant metabolism results in a large collection of known derivatives (7). One or more highly oxygenated aryl rings appear in many biologically active lignans (9). The similarity of the putative biosynthetic pathway to dianion oxidative coupling and the hierarchical increase in structural complexity of the lignans suggested that their preparation via this methodology could provide an opportunity to ascertain the scope and limitations of dianion coupling.

RESULTS AND DISCUSSION

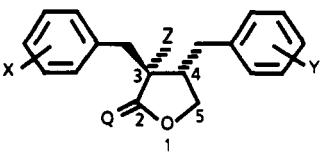
Dianion coupling provides a particularly convenient approach to symmetrical lignans (those with two identical side chains). Enterolactone [**3**] (10), a dibenzylbutane lignan produced in the human gut via bacterial fermentation of fiber and implicated in the prophylactic action of high fiber diets against colon cancer (11), was prepared in 50% overall yield by a seven-step dianion coupling sequence (12) beginning with a commercially available cinnamic acid. Wikstromol [**4**] (13), a lignan possessing significant antitumor activity, has been synthesized (14) in racemic form by a similar nine-step dianion coupling sequence proceeding in 29% overall yield from commercially available starting material. Hinokinin [**5**] (15) is readily made (6) in 60% overall yield from 3,4-(methylenedioxy)hydrocinnamic acid in a sequence also involving, as its key step, dianion coupling.



1 2

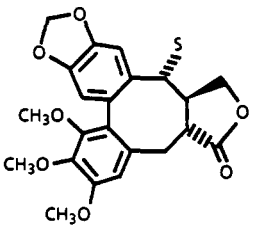
SCHEME 1

In order to carry out total syntheses of more complex, unsymmetrical lignans such as burseran [**6**] (16), deoxypodorhizon [**7**] (17), isostegane [**8**] (18), and steganacin [**9**] (19,20) via dianion-mediated chemistry, a necessary prerequisite is the use of an α-iodinated intermediate. Because retro-synthetic analysis suggested the availability of all four of these target molecules from a common precursor **10** and because traditional routes (21) to **10** were unsuccessful, considerable attention was devoted to the preparation of this compound (22). Eventually, two procedures were found that give crude **10** in comparable purity and yield (22). Due to moderate thermal- and photosensitivity, each batch of freshly prepared **10** was used without further purification once ^{1}H-nmr analysis had confirmed its identity.



1

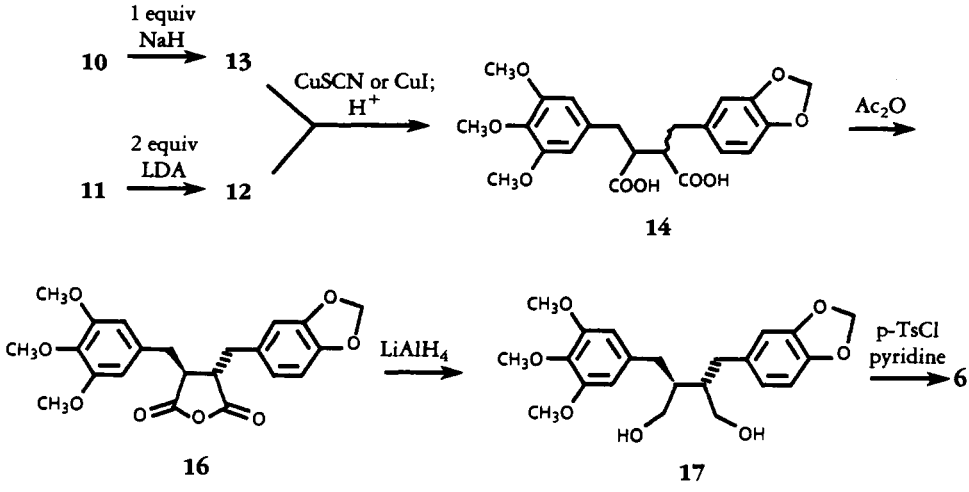
3 X=Y=3-OH, Z=H, Q=(=O)
4 X=Y=3-OMe, 4-OH; Z=OH; Q=(=O)
5 X=Y=3,4-(methylenedioxy); Z=H; Q=(=O)
6 X=3,4,5-trimethoxy; Y=3,4-(methylenedioxy); Z=H; Q=H,H
7 X=3,4,5-trimethoxy; Y=3,4-(methylenedioxy); Z=H; Q=(=O)



8 S=H
9 S=OAc

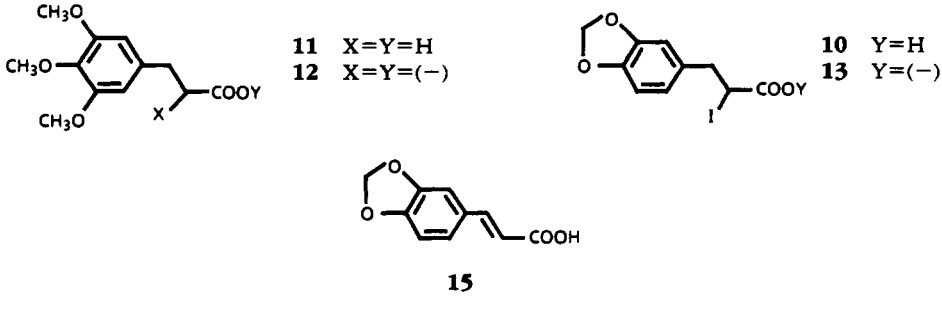
Burseran [**6**], a lignan natural product exhibiting modest antitumor activity, was first isolated by Cole *et al.* (16) from *Bursera microphylla*. Because there was some initial question as to the relative configuration of the two chiral centers in burseran, Tomioka *et al.* (23,24) synthesized both cis and trans diastereoisomers of burseran in optically pure form and found, by actual comparison, that the naturally occurring product is trans. Recently, another efficient asymmetric synthesis of burseran (as well as a number of other lignans) was reported by Rehnberg and Magnusson (25).

Possessing a tetrahydrofuran heterocycle backbone to which are appended differently substituted vicinal benzyl side chains, burseran is an obvious candidate for a dianion coupling that employed intermediates derived from two carboxylic acid substrates: α-iodoacid [**10**] and the commercially available acid **11**. In separate flasks, **11** is converted into dianion **12** while iodoacid [**10**] is transformed into its sodium salt **13**. Addition of **12** to **13** via cannula transfer, followed by routine workup, affords the crude diacid **14** as a mixture of diastereoisomers (Scheme 2).



SCHEME 2

Unfortunately, the above conditions generate only a modest yield of coupling product diacid **14**. Major contaminants are significant (15–35%) amounts of both the starting carboxylic acid [**11**] and the cinnamic acid elimination product **15**. Apparently, the carboxylic acid dianion is sufficiently basic that the rate of dehydrohalogenation of **13** (in spite of unfavorable electrostatics) competes favorably with the rate of coupling. In a control experiment, recovery, by acidification, of the α-iodocarboxylate suspension as unchanged **10** demonstrates that the NaH is not responsible for the dehydrohalogenation. Besides the loss of valuable α-iodoacid by this elimination pathway, the resulting cinnamic acid **15** possesses solubility characteristics similar to those of the diacid mixture **14**, thereby rendering recrystallization or trituration completely ineffective. Chromatographic procedures (tlc and flash chromatography) were unsatisfactory because of severe streaking and lack of satisfactory resolution of the various carboxylic acid components. Considerable improvement in the ratio of coupling to elimination was obtained by the addition of several equivalents of anhydrous LiCl to the suspension of **13** prior to addition of dianion **12**. Even more effective was the addition of 3–10 mol % of CuSCN or CuI (22). With this latter modification in procedure, conversion of the dianion/monoanion mixture into the desired coupling product **14** occurs, accompanied by no more than very minor levels (ca. 2–3%) of the undesired cinnamic acid **15** and the starting carboxylic acid **11**.



The crude diacid mixture **14** was heated at reflux with a large excess of Ac_2O. This operation smoothly epimerized the substituted benzyl chains into the thermodynami-

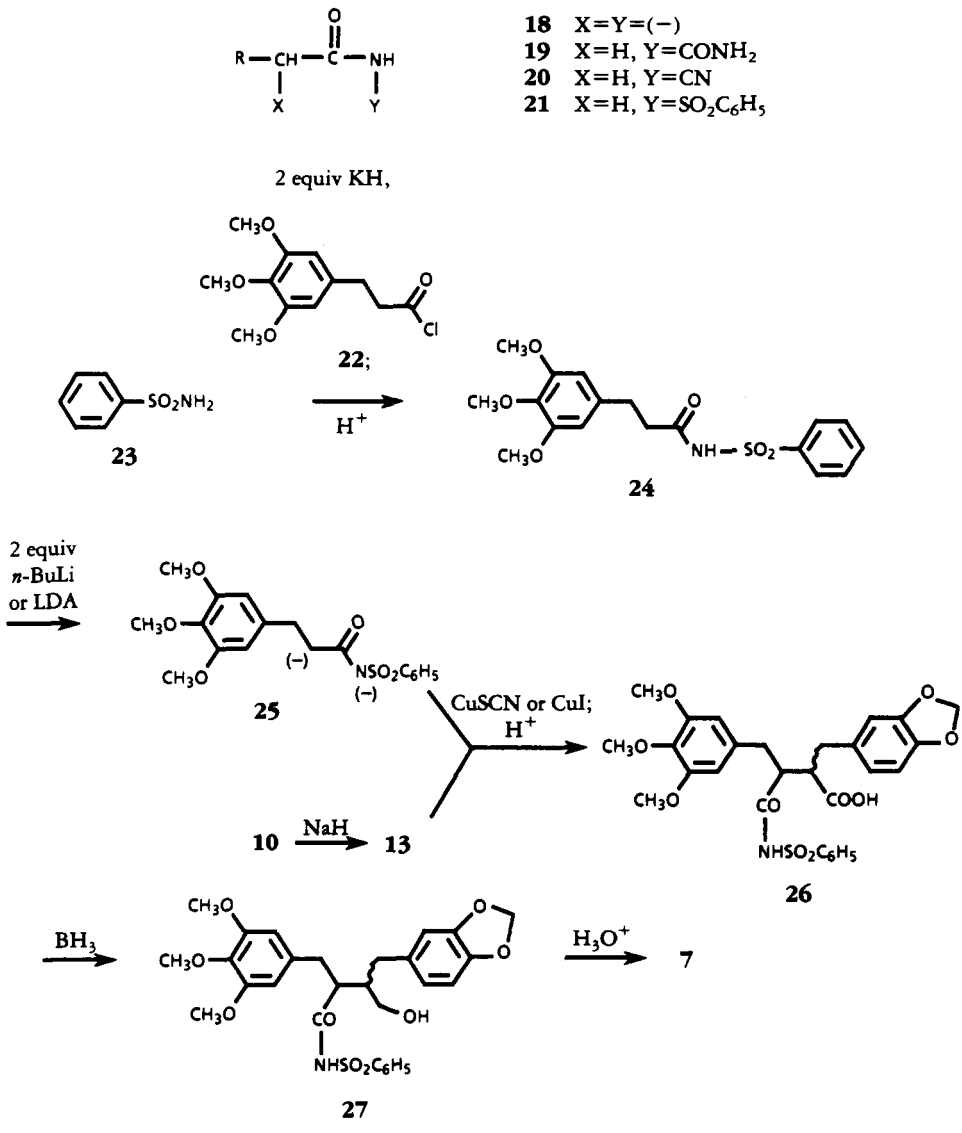
cally more stable (26) trans diastereoisomer with concomitant generation of the desired cyclic anhydride **16**. The anhydride, in turn, was readily reduced to diol **17** by treatment with $LiAlH_4$. The overall conversion from carboxylic acid **11** to **17** was 69%. Because this same diol (but in optically active form) had also been employed as an intermediate in Koga's synthesis (24) of burseran, preparation of racemic **17** constitutes a formal relay synthesis of racemic burseran [**6**]. However, as an additional check, our diol sample was carried on, using Koga's conditions (24), to give a sample of racemic **6** (in 67% yield) that was identical in spectroscopic properties to authentic material.

Deoxypodorhizon [**7**] was first isolated by McDoniel and Cole (17). This natural product has been employed as a crucial precursor in the route of Koga and co-workers (19, 20, 27–29) to steganacin. Several earlier syntheses of deoxypodorhizon employed a preformed butyrolactone ring. For example, Damon *et al.* (18) carried out an efficient Michael-type approach to **7** using a butenolide as the acceptor and a dithiane anion as the nucleophile while Tomioka *et al.* (29) separately prepared both enantiomers of **7** using chiral butyrolactone precursors.

In our strategy, the butyrolactone ring was to be generated as the final step in a sequence that begins with dianion coupling. Such coupling methodology should permit complete control over which one of the two possible substituted benzyl side chains will be located on the carbon atom adjacent to what, ultimately, will become the lactone carbonyl. This necessitated devising carbonyl-based functionality that can be converted into a dianion able to react with an alpha-iodocarboxylate yet which would still allow the two carbonyls in the resulting coupling product to be chemodifferentiated during generation of the target butyrolactone. One way to chemodifferentiate two coupling units, both at the carboxylic acid oxidation state, is for one partner to be a carboxylic acid and for the other to be a carboxamide. Because the published conditions for borane reduction of carboxylic acids (30) are slightly less vigorous than the reported conditions for carboxamide reduction (31), our strategy revolved around finding conditions to achieve controlled reduction when the functional groups are vicinal to one another.

Thus, one obvious possibility for dianion coupling was to react a simple primary amide dianion **18** with iodocarboxylate salt **13**. From the perspective of known relative rates of amide reduction (31), a primary amide was the optimal carboxamide choice. However, background experiments disclosed that the corresponding dianion species prepared from such an unsubstituted amide was far too basic and its reaction with **13** led to numerous by-products. By placing electron withdrawing groups on the amide nitrogen, the overall pKa of the two deprotonations is significantly lowered. Consequently, the preparation and dianion formation from a variety of amide derivatives including acylureas such as **19** (32), acylcyanamides such as **20** (33), and acylsulfonamides such as **21** (34) was examined. Acylsulfonamides, with their first deprotonation pKa of ca. 5 (35), proved the most satisfactory dianion precursors. Easily prepared and generally highly crystalline (34), acylsulfonamides can be converted into their corresponding dianions either with LDA or with *n*-BuLi.

Reaction of acid halide **22** with benzenesulfonamide [**23**] in the presence of 2+ equiv of KH gives acylsulfonamide **24** as an easily purified colorless solid (Scheme 3). Upon treatment with 2+ equiv of LDA, acylsulfonamide **24** is converted into its dianion **25**. The presence of Cu(I) salts also significantly diminishes the yield of elimination by-product **15** during dianion coupling of **25**. When a solution of dianion **25** is added, via cannula, to iodoacid carboxylate **13** and 3–10 mol % of CuI followed by simple workup, acid/acylsulfonamide **26** is produced as a mixture of diastereoisomers. When dianion **25** is generated by low temperature addition of 2+ equiv of *n*-BuLi and then added to a suspension of carboxylate **13** and CuI, much less coupling product **26** and much more cinnamic acid **15** are formed. The observation of more satisfactory Cu(I)-



SCHEME 3

mediated dianion behavior with LDA-generated dianion versus *n*-BuLi-generated dianion have also been reported by Katzenellenbogen and Crumine (36).

Model studies supporting selective reduction of a carboxylate carbonyl in the presence of an acylsulfonamide carbonyl were very encouraging (34). However, later investigations examining the generality of this approach for examples having substituents at both the 3 and the 4 position of the butyrolactone (numbering as shown on structures **3**–**7**) unequivocally demonstrate that chemoselectivity in the reduction process requires an individualized optimization effort (37). Thus, the reaction conditions for the deoxypodorhizon sequence were specifically tailored just for this target.

Borane reduction of pre-prepared mixtures of acylsulfonamide and carboxylic acid mono-functionalized substrates revealed acceptable selectivity in favor of rapid carboxylic acid reduction. It is only when the acylsulfonamide and the carboxylic acid moieties are present as vicinal functionality that a serious decrease in chemoselectivity

occurs. For the deoxypodorhizon sequence, careful optimization efforts eventually made possible reasonably efficient conversion to the desired hydroxymethyl derivative **27**. We found that low temperature treatment with a slight excess of borane in a solvent mixture consisting largely of Et_2O (with just enough THF to solubilize the substrate (in approximately a 6:1 ratio) leads to optimal selectivity in the reduction. We speculate that the vicinal carboxylic acid and acylsulfonamide groups, when crowded, may undergo a hydrogen bonding interaction that interferes with the chemoselectivity of the borane addition but which is also influenced by the Lewis basicity of the solvent employed.

Because a mixture of diastereoisomers forms during the dianion coupling, because the borane reduction is only moderately selective even under optimal conditions, and because the crude product mixtures are too polar for separation via any process other than reversed-phase hplc, which is preparatively impractical, it became convenient to carry on the reaction product as an unpurified mixture until a final chromatography. During the acid hydrolysis step, the acylsulfonamide is converted into a carboxylic acid group that spontaneously lactonizes via attachment to the adjacent hydroxymethyl moiety. Epimerization of the substituted benzyl side chain alpha to the carbonyl also proceeds, thereby producing relatively pure (>95% homogeneity by ^1H nmr) *trans*-disubstituted butyrolactone deoxypodorhizon [**7**]. Actual comparison with an authentic sample of deoxypodorhizon confirms the synthesis of racemic deoxypodorhizon. After final purification, the overall yield is 50%.

Deoxypodorhizon, when treated with VOF_3, is known to undergo clean transformation to isostegane [**8**] (18,20). Success with this reaction provided a check as to the identity of our synthetic deoxypodorhizon. By comparison with an authentic sample of isostegane, our synthetic racemic isostegane was determined to be indistinguishable from "authentic" isostegane. Because Koga and co-workers also have converted isostegane into steganacin via a published (19, 20, 27–29) route, our obtaining both deoxypodorhizon and isostegane constitutes a formal relay synthesis to steganacin [**9**] itself via use of dianion coupling methodology.

Even though numerous asymmetric syntheses have been reported for the various lignan targets **6**, **7**, **8**, and **9** (19, 20, 23–25, 27–29), one should point out the obvious, as yet unmet, challenge of fashioning an asymmetric approach involving dianion coupling methodology. Nevertheless, the highly convergent nature of the dianion-based strategy remains attractive by virtue of affording short sequences to racemic samples of relatively complex lignans.

In conclusion, this work establishes that a common iodocarboxylic acid can serve both as a precursor to the tetrahydrofuran burseran and as a key starting material for a synthetic series that leads in a linear sequence to deoxypodorhizon, isostegane, and steganacin.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined with a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. ^1H- and ^{13}C-nmr spectra were recorded on Bruker and Nicolet spectrometers with TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer Model 1600 FT spectrophotometer. Mass spectra were determined with a Kratos MS-801 DS55 spectrometer. All reactions were run under dry N_2 unless otherwise specified. Glassware for the dianion reactions was assembled hot from a 115° oven, purged with N_2, and then flame-dried under vacuum. THF was distilled from sodium benzophenone ketyl immediately before use. Diisopropylamine was distilled from BaO immediately prior to use. Ligroin, $CHCl_3$, and EtOAc used in purifications were distilled before use. All reagents and starting materials are commercially available.

DIACID **14**.—A 50 ml Schlenk tube equipped with a stirring bar was flame-dried several times while being exposed to alternate vacuum and N_2 purge. To the flask were added dry THF (15 ml) and diiso-

propylamine (0.42 ml, 3.0 mmol). The solution was cooled to −20° whereupon *n*-BuLi (1.6 M in hexane) (1.9 ml, 3.04 mmol) was added over 1–2 min. The apparatus was transferred to a 0° ice-bath for 1 h. The LDA solution was then cooled to −78°, and a solution of 3-(3,4,5-trimethoxyphenyl)propionic acid (0.361 g, 1.5 mmol) in THF (10 ml) was added. The dianion formation was continued at −78° for 1 h and at 0° for 6 h (solution A).

In a separate operation, to a flame-dried 100 ml three-neck round-bottom flask under N_2 was added NaH (60% oil dispersion, 0.066 g, 1.65 mmol). The hydride salt was washed with ligroin (3 × 10 ml) and dried under N_2 to afford a free-flowing gray powder. THF (15 ml) was added, and the suspension was cooled to −25° whereupon iodoacid **10** (0.480 g, 1.5 mmol) dissolved in THF (5 ml) was added via syringe. The bath was allowed to warm to −5° during the addition. The resulting suspension was stirred from −5° to 5° for 35 min and then for a further 30 min at 0° during which time it became a whitish suspended solid. The suspension was cooled to −78°, and CuSCN (0.009 g, 0.075 mmol) was added against a positive pressure of N_2. The suspension was stirred a further 10 min at −78° (suspension A).

By cannula, the dianion (solution A) was added to the carboxylate (suspension A) over 42 min. The cooling bath warmed to −60° during the addition. The reaction mixture was recooled to −78° and then allowed to warm and stay at 5° over 3.5 h. The olive suspension was quenched by the slow addition of 7 ml of 1 N HCl and allowed to stir at room temperature overnight. The resulting yellow suspension was diluted with EtOAc and transferred to a separatory funnel where the layers were partitioned. The organic phase was washed with saturated $NaHCO_3$ (5 ml) and then with saturated brine (2 × 5 ml). The organic layer was dried over $MgSO_4$ and filtered, and the volatiles were removed to afford a pale yellow amorphous foam that was generally carried on to the anhydride further without purification: ^{1}H nmr ($CDCl_3$, DMSO-d_6, 300 MHz) δ 6.7 (m, 3H), 6.43 (s, 2H), 5.91 (s, 2H), 3.82 (s, 6H), 3.78 (s, 3H), 3.00–2.78 (m, 6H) (the 2H for COO*H* are apparently too broad to observe); ^{13}C nmr ($CDCl_3$, DMSO-d_6, 75 MHz) δ 174.8, 174.8, 152.7, 147.3, 145.9, 136.1, 134.7, 132.6, 121.8, 109.2, 107.9, 105.9, 100.6, 60.4, 55.8, 50.0, 49.6, 36.4, 35.9; ir ν max (KBr) cm^{-1}3500–2800 (br), 1736, 1700, 1589, 1507, 1449, 1422, 1244, 1193, 1127, 1040, 1006, 929; hreims *m/z* [M]$^+$ 432.1439 (calcd for $C_{22}H_{24}O_9$, 432.1420). Based on precedent (6,12), the stereochemistry was tentatively assigned as trans.

ANHYDRIDE **16**.—Into a 100 ml round-bottom flask equipped with a stirring bar, reflux condenser, and an N_2 inlet was placed the crude diacid coupling product (assumed to be 1.5 mmol) and Ac_2O (25 ml, 265 mmol). The apparatus was carefully flushed with N_2, and the resulting amber solution was brought to gentle reflux. Heating under N_2 was maintained for 30 h. Residual Ac_2O/HOAc was removed by vacuum distillation (0.5 torr, 60°) to afford a brown syrup that was converted directly to the diol without further purification: ir ν max ($CHCl_3$) cm^{-1} 2915, 1856, 1780, 1587, 1500, 1485, 1440, 1235, 1128, 1080, 1000; eims *m/z* [M]$^+$ 414.

(±)-DIOL **17**.—The crude anhydride adduct (assumed to be 1.5 mmol based on the starting carboxylic acid stoichiometry) present as a thick brown syrup in a 100 ml round-bottom flask equipped with a stirring bar, reflux condenser, and nitrogen inlet was dissolved in THF (25 ml), and the solution was cooled to 0° with an ice-H_2O bath. An excess $LiAlH_4$ (95%, 0.210 g, 5.25 mmol) was sprinkled into the flask in portions against positive N_2 pressure, whereupon a vigorous exotherm occurred. After the reaction subsided, the resulting grayish suspension was stirred at 0° for 15 min, at room temperature for 5 min, and then at gentle reflux (oil bath temperature 60°) for 15 h. The light gray-green suspension was then cooled to 0°. Over a 20-min period, the reaction mixture was quenched by the careful (!) addition of H_2O (10 ml). The volatiles were removed on a rotary evaporator to give a yellow syrup to which was added EtOAc (80 ml) and 1 N HCl (15 ml). The layers were partitioned in a separatory funnel. The aqueous phase was further extracted with EtOAc (2 × 35 ml). The organic phases were combined, washed with saturated brine (10 ml), dried over $MgSO_4$, and filtered, and the solvent was removed at reduced pressure to afford a yellow oil. Purification of the crude diol was accomplished via flash chromatography [20 g Si gel, 200–400 mesh, elution with a gradient varying from $CHCl_3$-Et_2O (9:1) to $CHCl_3$-Et_2O (3:1)]. The diol was initially obtained as a colorless oil homogeneous by tlc and spectroscopy (0.419 g, 69%). An analytical sample was obtained by recrystallization from EtOAc/ligroin (mp 114–116°): ^{1}H nmr ($CDCl_3$, 300 MHz) δ 6.72–6.56 (m, 3H), 6.36 (s, 2H), 5.91 (s, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.80–3.20 (m, some overlap with methoxy protons, 6H), 2.79–260 (m, 4H), 2.00–1.87 (br s, 2H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 153.1 (t), 147.6 (s), 145.7 (s), 136.3 (s), 134.3 (s), 121.9 (d), 109.3 (d), 108.1 (d), 105.9 (d), 100.8 (t), 60.9 (q), 60.5 (t), 60.5 (t), 56.1 (q), 44.1 (d), 43.7 (d), 36.6 (t), 35.9 (t) [^{13}C nmr identical to that reported by Tomioka *et al.* (24)]; ir ν max (KBr) cm^{-1}3251 (br), 2939, 2838, 1591, 1504, 1486, 1456, 1434, 1371, 1328, 1240, 1193, 1130, 1033, 926, 816; eims *m/z* 404, 182 (100%), 135, 105, 91, 77; hreims *m/z* [M]$^+$ 404.1849 (calcd for $C_{22}H_{28}O_7$, 404.1835). Found C 65.35, H 7.09; calcd for $C_{22}H_{28}O_7$, C 65.33, H 6.98%.

(±)-BURSERAN [**6**].—To a 50-ml round-bottom flask equipped with a stirring bar and an N_2 inlet

was added pyridine (4 ml) and diol (0.202 g, 0.5 mmol). The flask was cooled to 0° using an ice-H_2O bath. *p*-Toluenesulfonyl chloride (0.104 g, 0.55 mmol) was then added to the well-stirred reaction mixture. After 10 min at 0°, the ice-H_2O bath was removed and the mixture was kept at room temperature for 1.5 h, heated at reflux (oil bath temperature 125°) for 4 h, and kept at room temperature overnight. The light brown solution was cooled to 0° and acidified with 6N HCl (approximately 7 ml was required). The reaction mixture was transferred to a separatory funnel and extracted with Et_2O (3 × 25 ml). The combined organic layers were washed with H_2O (3 × 5 ml), at which time the pH of the aqueous phase was near-neutral. The organic layer was dried over $MgSO_4$ and filtered, and the solvents were removed to afford a yellowish syrup. Purification was accomplished via dry cc using a 5% gradient beginning with $CHCl_3$-ligroin (1:1) to provide racemic burseran as a colorless oil (0.129 g, 67%) that gradually turned pale yellow on exposure to air: ^{1}H nmr ($CDCl_3$, 300 MHz) δ 6.7–6.5 (m, 3H), 6.28 (s, 2H), 5.92 (dd, J = ca. 1.5 Hz, 2H), 3.96–3.76 (m, 2H), 3.89 (s, 6H), 3.82 (s, 3H), 3.57–3.48 (m, 2H), 2.68–2.50 (m, 4H), 2.30–2.15 (m, 2H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 153.1 (s), 147.6 (s), 145.9 (s), 136.3 (s), 136.1 (s), 134.1 (s), 121.4 (d), 108.9 (d), 108.0 (d), 105.5 (d), 100.9 (t), 73.2 (t), 73.2 (t), 60.8 (q), 56.0 (q), 46.6 (d), 46.4 (d) 39.9 (t), 39.2 (t) [^{13}C nmr spectrum identical to that reported by Tomioka *et al.* (24)].

3-(3,4,5-TRIMETHOXYPHENYL)PROPIONIC ACID CHLORIDE [**22**].—To a 100-ml recovery flask were added 3-(3,4,5-trimethoxyphenyl)propionic acid (6.00 g, 24.97 mmol), 100 ml of dry, reagent grade C_6H_6, and oxalyl chloride (4.50 ml, 51.6 mmol). The flask was capped lightly and the mixture was allowed to stand for 2.5 h with periodic swirling. The suspended acid gradually dissolved, gas evolution decreased, and a yellow solution resulted. Volatiles were removed by rotary evaporation to give a syrup which crystallized when pumped at high vacuum. The purity of the acid chloride was checked by ir. The crude material was used directly for the preparation of the acylsulfonamide: ^{1}H nmr ($CDCl_3$, 300 MHz) δ 6.41 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.21 (t, J = 7.5 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 173.1 (s), 153.4 (s), 136.7 (s), 134.4 (s), 105.2 (d), 60.8 (q), 56.1 (q), 48.7 (t), 31.4 (t); ir ν max (CCl_4) cm^{-1} 2980, 2920, 2820, 1800, 1585, 1500, 1455, 1415, 1350, 1325; eims *m/z* [M]$^+$ 258, 243, 222, 181, (100%), 179, 165, 151, 136.

N-BENZENESULFONYL-3-(3,4,5-TRIMETHOXYPHENYL)PROPIONAMIDE [**24**].—To a tared apparatus consisting of a 250-ml flask containing gas inlets equipped with stopcocks and a stirbar was added KH (35% in oil, 4.60 g, 40.1 mmol). The KH was washed with ligroin (5 × 10 ml) under N_2 and placed under high vacuum for 25 minutes to remove the last traces of ligroin. The pyrophoric (!), oil-free KH was a cream-colored, coarse, free-flowing powder. While keeping the apparatus under N_2, THF (50 ml) was added and the stirring bar was replaced with a mechanical stirrer. The resulting suspension was cooled to 0°, and benzenesulfonamide (3.00 g, 19.1 mmol) in THF (16 ml) was added with stirring over 3.5 min. The mixture was stirred at 0° for 3h, and the acid chloride (4.94 g, 19.1 mmol) in THF (16 ml) was added via syringe pump over 27 min. After warming to room temperature over 16 h, the mixture was a thick, creamy, off-white suspension. The reaction was now quenched by the dropwise addition of iPrOH (5 ml) followed by an additional 10 min of stirring. The volatiles were removed under vacuum. To the residue were added 50 ml of EtOAc, 25 ml of saturated $NaHCO_3$ solution, and 100 ml of H_2O. The mixture was poured into a separatory funnel and shaken, and the layers were separated. The aqueous layer was cooled to 0° and acidified carefully (foaming !) with concentrated HCl to a final pH of 1. After stirring for 0.5 h, the acidified layer was extracted with EtOAc (2 × 75 ml), and the combined EtOAc layers were washed with 20 ml of saturated brine. After drying over $MgSO_4$, the EtOAc was removed by rotary evaporation to give 6.665 g of a light yellow solid. This crude material was recrystallized from EtOAc in 2 crops to give the acylsulfonamide as a highly crystalline white solid (5.333 g, 73.6%): mp 116–117°; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 9.25 (br s, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.70–7.49 (m, 3H), 6.25 (s, 2H), 3.82 (s, 3H), 3.73 (s, 6H), 2.78 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 170.2 (s), 153.1 (s), 138.6 (s), 136.1 (s), 135.9 (s), 133.9 (d), 129.0 (d), 128.2 (d), 105.1 (d), ,60.9 (q), 56.0 (q), 38.1 (t), 30.5 (t); ir ν max ($CHCl_3$) cm^{-1} 3600–2700 (m, br), 1730 (s), 1600 (s); eims *m/z* 379, 238, 207, 181 (100%); hrms *m/z* [M]$^+$ 379.1091 (calcd for $C_{18}H_{21}NO_6S$, 379.1090). Found C 56.85, H 5.32; calcd for $C_{18}H_{21}NO_6S$, C 56.98, H 5.58%.

2-IODO-3-(3,4-METHYLENDIOXYPHENYL)PROPANOIC ACID [**10**].—Using either of the two standard literature methods (22), the desired iodoacid could be obtained as a light yellow solid whose purity was most easily assessed, on a routine basis, by ^{1}H nmr. The yield and purity of the iodoacid were essentially equivalent by either method of preparation: ^{1}H nmr ($CDCl_3$, 80 MHz) δ 6.85–6.55 (m, 3H), 5.9 (s, 2H), 4.47 (dd, J = 9, 7 Hz, 1H), 3.55–2.90 (m, 2H).

ACID-ACYLSULFONAMIDE [**26**].—To a 25-ml Schlenk tube containing a stirbar was added THF (5 ml). The THF was cooled to −78°, and diisopropylamine (0.31 ml, 2.2 mmol) and *n*-BuLi (1.5 M in hexane, 1.33 ml, 2.0 mmol) were added. After 5 min, the acylsulfonamide **24** (0.379 g, 1.00 mmol) in

THF (5 ml) was added to the LDA solution. The resulting solution was stirred at −78° for 0.5 h and then at 0° for 3 h to give a homogeneous green-yellow dianion solution (solution B).

Meanwhile, a 50-ml flask was flame-dried under a N_2 purge. When it had cooled, NaH (60% in oil, 0.048 g, 1.2 mmol) was added to the flask. The NaH was then washed with ligroin (2 × 2 ml). The last traces of ligroin were removed by an N_2 stream to give a fine gray powder. To the flask was added THF (5 ml). The resulting suspension was cooled to −19° (ice/salt), at which time iodoacid **10** (0.320 g, 1.00 mmol) in THF (5 ml) was added over 15 min. The mixture was stirred at 0° for 0.75 h to give a creamy white suspension that was then cooled to −78° (suspension B).

CuI (0.019 g, 0.1 mmol) was added to suspension B followed by stirring for 15 min at −78°. Then, by cannula, solution B (pre-cooled to 0°) was added to suspension B over 37 min. The mixture was slowly allowed to warm to 15° over 3 h, at which time saturated NH_4Cl solution (5 ml) was added to the reaction mixture. After 5 min, 1 N HCl was added and the layers were separated. The aqueous layer was extracted with Et_2O (20 ml). The combined organic layers were washed with 1 M $NaHSO_3$ (5 ml) and with saturated brine (5 ml), dried over $MgSO_4$, and filtered, and the volatiles were removed to give **26** as a yellow foam. The material, extremely polar by tlc (10% EtOAc: 90% ligroin), can be partially purified by trituration (Et_2O, then EtOAc) but was usually used in its crude form to prepare deoxypodorhizon: mp 183–184°; ^{1}H nmr ($CDCl_3$/DMSO-d_6, 300 MHz) δ 7.83–7.80 (m, 2H), 7.60–7.38 (m, 3H), 6.60–6.50 (m, 3H), 6.27 (s, 2H), 5.91 (s, 2H), 3.80 (s, 3H), 3.74 (s, 6H), 3.06–2.69 (m, 6H) (the 2H for N*H* and COO*H* are apparently too broad to observe); ^{13}C nmr ($CDCl_3$/DMSO-d_6, 75 MHz) δ 175.0 (s), 172.6 (s), 152.8 (s), 147.4 (s), 146.0 (s), 139.2 (s), 136.2 (s), 133.7 (s), 133.2 (d), 132.3 (s), 128.5 (d), 127.7 (d), 122.0 (d), 109.4 (d), 108.0 (d), 105.7 (d), 100.8 (t), 60.7 (q), 55.8 (q), 48.8 (d), 48.6 (d), 35.5 (t), 34.3 (t); ir ν max (Nujol) cm^{-1} 3240, 1730, 1710, 1595; eims *m/z* 414, 181 (100%), 157, 135, 93, 77; hreims *m/z* $[M - PhSO_2NH_2]^+$ 414.1353 (calcd for $C_{22}H_{22}O_8$, 414.1315). Found C 58.27, H 5.12, N 2.46; calcd for $C_{28}H_{29}NSO_{10}$, C 58.84, H 5.11, N 2.45.

(±)-DEOXYPODORHISON [**7**].—To a 25-ml two-neck round-bottom flask containing a stirbar was added the crude acid-acylsulfonamide **32** (0.200 g, ca. 0.35 mmol) followed by THF (2 ml) and Et_2O (8 ml). The resulting slightly cloudy yellow solution was cooled to 0°, and BH_3·THF (1.0 M in THF, 0.52 ml, 0.52 mmol) was added slowly (gas evolution noted). The mixture was allowed to warm to room temperature slowly overnight (after initial cooling in a crystallizing dish filled with ice H_2O). MeOH (5 ml) and concentrated HCl (10 drops in 2 ml THF) were added. The resulting solution was stirred again overnight at room temperature. The reaction mixture was diluted with H_2O (5 ml) and Et_2O (10 ml), and the layers were separated. The aqueous layer was extracted with Et_2O (10 ml), the combined organic layers were washed with saturated brine (5 ml), dried over $MgSO_4$, and filtered, and the volatiles were removed under reduced pressure to afford a yellow paste. Radial chromatography (1 mm Si gel plate, development with 8% Et_2O/92% CH_2Cl_2) provided racemic deoxypodorhizon as a glass (0.071 g, 50%): ^{1}H nmr ($CDCl_3$, 300 MHz) δ 6.75–6.65 (m, 1H), 6.55–6.45 (m, 2H), 6.36 (s, 2H), 5.94 (s, 2H), 4.18 (dd, J = 9, 7 Hz, 1H), 3.86 (dd, partially obscured, J = 9, 7 Hz, 1H), 3.83 (s, 9H), 3.00–2.85 (m, 2H), 2.70–2.40 (m, 4H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 178.4 (s), 153.2 (s), 147.9 (s), 146.4 (s, 136.8 (s), 133.3 (s), 131.5 (s), 121.5 (d), 108.7 (d), 108.2 (d), 106.2 (d), 101.0 (t), 71.1 (t), 60.8 (q), 56.1 (q), 46.4 (d), 41.0 (d), 38.3 (t), 35.2 (t) [identical ^{13}C nmr spectrum to that reported by Tomioka *et al.* (29)]; ir ν max ($CHCl_3$) cm^{-1} 1772 (s), 1595 (m); eims *m/z* 400, 283, 181 (100%), 135, 77; hreims *m/z* $[M]^+$ 400.1496 (calcd for $C_{22}H_{24}O_7$, 400.1522). Found C 65.77, H 5.91; calcd for $C_{22}H_{24}O_7$, C 65.99, H 6.04.

(±)-ISOSTEGANE [**8**].—To a 15-ml two-neck round-bottom flask equipped with a stirring bar, a rubber septum, and an N_2 inlet were added VOF_3 (0.084 g, 0.674 mmol) followed by CH_2Cl_2-TFA (4:1) (5 ml). The yellow suspension was cooled to 0°, and racemic deoxypodorhizon (0.045 g, 0.112 mmol) in CH_2Cl_2 (2 ml) was added dropwise over 8 min. Upon addition of the lactone, the reaction mixture immediately became dark brown. After 1 h at 0° and 2 h at room temperature, the solution was recooled to 0° and quenched slowly by the dropwise addition of saturated Na_2CO_3 solution (4 ml) with vigorous concomitant gas evolution. Et_2O (10 ml) was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (10 ml). The combined organic layers were washed with saturated brine (5 ml), dried over $MgSO_4$, and filtered, and the volatiles were removed to give a brown oil. Racemic isostegane was isolated as a colorless oil (0.019 g, 43% yield) by filtration through SiO_2 (1 g) with elution by $CHCl_3$ (40 ml) followed by radial chromatography (1 mm Si gel plate, development with 8% $CHCl_3$/92% CH_2Cl_2): ^{1}H nmr ($CDCl_3$, 300 MHz) δ 6.70 (s, 1H), 6.63 (s, 1H), 6.62 (s, 1H), 6.01 (d, J = 1.2 Hz, 1H), 5.98 (d, J = 1.2 Hz, 1H), 4.37 (dd, J = 8.4, 6.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.78 (dd, J = 10.8, 8.4 Hz, 1H), 3.57 (s, 3H), 3.12 (d, J = 13.2 Hz, 1H), 2.64 (d, J = 12 Hz, 1H), 2.45–2.05 (m, 4H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 176.5, 153.3, 151.8, 147.6, 145.9, 140.8, 136.0, 132.3, 128.3, 126.4, 111.7, 108.8, 107.5, 101.2, 70.0, 60.9, 60.8, 56.0, 50.0, 46.7, 34.1, 32.3

[identical ^{13}C nmr spectrum to that reported by Tomioka *et al.* (27)]; ir ν max ($CHCl_3$) cm^{-1} 3000, 2950, 2910, 1780, 1600, 1485, 1405, 1340, 1325; eims *m/z* $[M]^+$ 398, 317, 263, 232, 101, 84 (100%).

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Elsa U. Pardee Foundation and the American Cancer Society for this project. Preliminary work was done with the support of the National Institutes of Health (PHS grant RO1 CA40105 awarded by the National Cancer Institute, DHHS) and by the donors of the Petroleum Research Fund (PRF grant 17928-AC1). S.L.F. and D.F.F. thank the University Research Council of the University of Cincinnati for summer fellowships. The 250 MHz spectrometer used in this research was acquired in part with funds from an Ohio Academic Challenge grant. The Kratos mass spectrometer used in this research was purchased with the aid of an NSF instrumentation grant (PCM-8219912). We thank Prof. K. Koga for providing copies of spectra and comparison samples. Finally, the authors thank Mrs. Elaine Seliskar for the typing and the drawings in this manuscript.

LITERATURE CITED

1. D.F. Fry, "The Application of Dianion Chemistry to Natural Product Synthesis," Ph.D. Thesis, University of Cincinnati, Cincinnati, Ohio, 1988.
2. J.L. Belletire and E.G. Spletzer, *Tetrahedron Lett.*, **27**, 131 (1986).
3. J.L. Belletire, E.G. Spletzer, and A.R. Pinhas, *Tetrahedron Lett.*, **25**, 5969 (1984).
4. P. Renaud and M.A. Fox, *J. Org. Chem.*, **53**, 3745 (1988).
5. J. Fuhrhop and G. Penzlin, "Organic Synthesis: Concepts, Methods, Starting Materials," Verlag Chemie, Weinheim, 1984.
6. J.L. Belletire and D.F. Fry, *J. Org. Chem.*, **52**, 2549 (1987).
7. C.B.S. Rao, "Chemistry of Lignans," Andhra University Press, Andhra Pradesh, 1978.
8. T.A. Geissman and D.H. Crout, "Organic Chemistry of Secondary Plant Metabolism," Freeman, Couper, & Co., San Francisco, 1969, pp. 398–399.
9. W.D. MacRae and G.H.N. Towers, *Phytochemistry*, **23**, 1207 (1984).
10. G. Cooley, R.D. Farrant, D.N. Kirk, S. Patel, S. Wynn, M.J. Buckingham, G.E. Hawkes, M.B. Hursthouse, A.M.R. Galas, A.M. Lawson, and K.D.R. Setchell, *J. Chem. Soc., Perkin Trans. 2*, 489 (1984).
11. M. Axelson, J. Sjovall, B.E. Gustaffson, and K.D.R. Setchell, *Nature (London)*, **298**, 659 (1982).
12. J.L. Belletire and S.L. Freemont, *Tetrahedron Lett.*, **27**, 127 (1986).
13. J.L. Belletire, D.M. Ho, and D.F. Fry, *J. Nat. Prod.*, **53**, 1587 (1990).
14. J.L. Belletire and D.F. Fry, *J. Org. Chem.*, **53**, 4724 (1988).
15. E. Wenkert, H.E. Gottlieb, O.R. Gottlieb, M.O. Da S Pereira, and M.D. Formiga, *Phytochemistry*, **15**, 1547 (1976).
16. J.R. Cole, E. Bianchi, and E.R. Trumbull, *J. Pharm. Sci.*, **58**, 175 (1969).
17. P.B. McDoniel and J.R. Cole, *J. Pharm. Sci.*, **61**, 1992 (1972).
18. R.E. Damon, R.H. Schlessinger, and J.F. Blount, *J. Org. Chem.*, **41**, 3772 (1976).
19. K. Tomioka, T. Ishiguro, and K. Koga, *Tetrahedron Lett.*, **21**, 2973 (1980).
20. K. Tomioka, T. Ishiguro, Y. Itaka, and K. Koga, *Tetrahedron*, **40**, 1303 (1984).
21. J. March, "Advanced Organic Chemistry: Reactions, Mechanism, and Structure," 3rd ed. John Wiley & Sons, New York, 1985, pp. 531–532.
22. J.L. Belletire, S.L. Fremont, and D.F. Fry, *Synth. Commun.*, **18**, 699 (1988).
23. K. Tomioka, T. Ishiguro, and K. Koga, *J. Chem. Soc., Chem. Commun.*, 652 (1979).
24. K. Tomioka, T. Ishiguro, and K. Koga, *Chem. Pharm. Bull.*, **33**, 4333 (1985).
25. N. Rehnberg and G. Magnusson, *J. Org. Chem.*, **55**, 4340 (1990).
26. S.A.M.T. Hussain, W.D. Ollis, C. Smith, and J.F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1480 (1975).
27. K. Tomioka, H. Mizuguchi, T. Ishiguro, and K. Koga, *Chem. Pharm. Bull.*, **33**, 121 (1985).
28. T. Ishiguro, H. Mizuguchi, K. Tomioka, and K. Koga, *Chem. Pharm. Bull.*, **33**, 609 (1985).
29. K. Tomioka, H. Mizuguchi, and K. Koga, *Chem. Pharm. Bull.*, **30**, 4304 (1982).
30. N.N. Yoon, C.S. Pak, H.C. Brown, S. Krishnamurthy, and T.P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
31. H.C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973).
32. J.L. Belletire and M. Hiller, *Synth. Commun.*, **19**, 3543 (1989).
33. J.L. Belletire, *Synth. Commun.*, **18**, 2063 (1988).
34. J.L. Belletire and E.G. Spletzer, *Tetrahedron Lett.*, **27**, 131 (1986).
35. T.K. Schaaf and H.-J. Hess, *J. Med. Chem.*, **22**, 1340 (1979).
36. J.A. Katzenellenbogen and A.L. Crumine, *J. Am. Chem. Soc.*, **98**, 4925 (1976).
37. J.L. Belletire and N.O. Mahmoodi, *Synth. Commun.*, **19**, 3371 (1989).

Received 1 July 1991