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Synthesis and Intramolecular Reactions of *trans*-Cyclohexyl-1,2-bisacrylate

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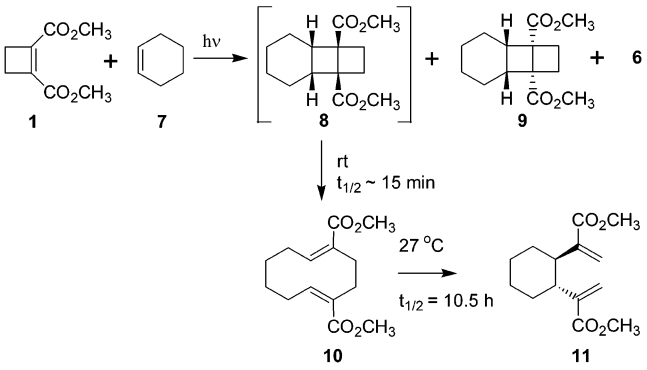
Received September 2, 2003

Abstract: Photocycloaddition of dimethyl cyclobut-1-ene-1,2-dicarboxylate (**1**) with cyclohexene (**7**) afforded two photoadducts **8** and **9** in 44% and 28% yields, respectively. Spontaneous thermal isomerization of **8** gave (4*Z*,10*Z*)-dimethyl cyclodeca-4,10-diene-1,4-dicarboxylate (**10**), which subsequently isomerized to produce *trans*-1,2-cyclohexanebis-α-acrylic acid dimethyl ester **11**. Hydride reduction of the bisacrylate **11** gave the *trans*-octahydro-1*H*-inden-2-ols **12a** and **15** via a novel, stereoselective, intramolecular reaction. Reaction of the bisacrylate **11** with methyllithium afforded the bis-tertiary alcohol **16**. In contrast, lithium dimethylcuprate reacted with the bisacrylate **11** to give the *trans*-hexahydro-1*H*-inden-2-one **17** in high yield via a novel, stereoselective, intramolecular reaction.

Intramolecular reactions afford a high degree of stereochemical control for organic reactions.[1] However, for intramolecular reactions to occur, close proximity of the reactive functional groups is required. One method for generating functional groups in close proximity to each other is by the use of photocycloaddition/fragmentation reactions.[2] Photocycloaddition/fragmentation reactions via [2 + 2] and [4 + 4] cycloadditions have been the topic of a number of recent reviews.[3,4] An advantage of the [2 + 2] photocycloaddition reaction is the generation of the strained cyclobutane photoproduct. The release of strain energy can provide a driving force for subsequent reactions that can be directed by suitable substitution, leading to useful rearranged and more stable products.[3,4]

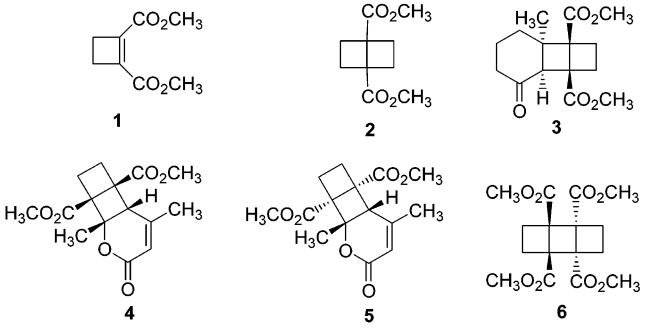
Dimethyl cyclobutene-1,2-dicarboxylate (**1**) has been photoadded to both acyclic[5] and cyclic olefins[6,7] to yield photoadducts **2**−**5** as well as **6**, the photodimer of **1**. All of these photoadducts contain a stable 1,4-dimethoxycarbonylbicyclo[2.2.0]hexane substructure. In this paper we discuss the photocycloaddition of **1** to cyclohexene (**7**) to yield two photoadducts **8** and **9** in 44% and 28% yields, respectively, containing the 1,4-dimethoxycarbonylbicyclo[2.2.0]hexane substructure. The photoadduct **8** thermally isomerizes to the 1,5-cyclodecadiene **10**, which subsequently undergoes a Cope rearrangement to a 1,2-bisacrylate system **11**. This 1,2-bisacrylate system **11** has been subjected to a variety of hard and soft nucleophiles and reducing reagents resulting in novel, stereoselective, intramolecular reactions.

Photocycloaddition of dimethyl cyclobutene-1,2-dicarboxylate (**1**) to cyclohexene (**7**) afforded two photoadducts *cis*,*syn*,*cis*-**8** and *cis*,*anti*,*cis*-**9**, together with the cis,anti,-cis photodimer **6** in 44%, 28%, and 11% yields, respectively. The cis,syn,cis photoadduct **8** has a transient existence (estimated half-life of 15 min at room temperature) before it isomerizes thermally to the monocyclic diene **10**. This cyclodeca-1,5-diene **10** is also unstable (measured half-life of 10.5 h at 300 K) before it undergoes a Cope rearrangement to yield the *trans*-bisacrylate **11** in quantitative yield. In a single experiment over the period of 16.5 h, the disappearance of the cyclodeca-1,5-diene **10** appears to be linear. The first-order kinetics are shown in Table 1 and Graph 1 of the Supporting Information. The structure of **8** is based on its method of synthesis and its ready isomerization to the diene **10**. The cis,anti,cis stereochemistry of the other photoadduct **9** is based on its NOESY spectrum. A correlation is observed between a bridge methine hydrogen and one of the methylene hydrogens on the cyclobutane ring.



1 7 8 9 6 10 11

Due to symmetry, the stereochemistry of the bisacrylate **11** was difficult to determine by NMR. The easiest way to differentiate between *cis*- and *trans*-**11** was by chiral HPLC. The cis compound is a meso form and will give one peak when chromatographed on a chiral HPLC column whereas the trans compound is racemic and will give two peaks. Chiral HPLC on **11** gave two peaks resulting from a mixture of diastereomers, thereby show-



1 2 3 4 5 6

‡ Deceased August 7, 1973.

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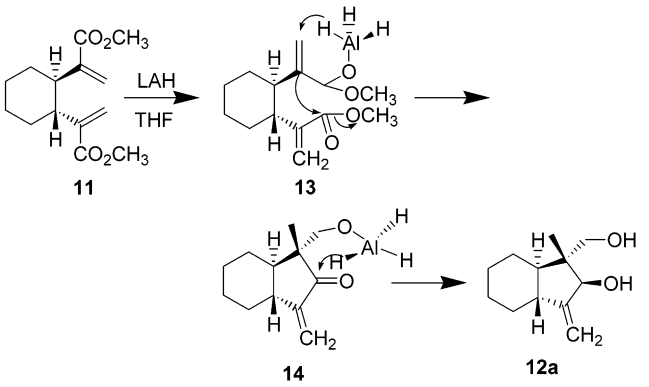
10.1021/jo035281i CCC: $27.50 © 2004 American Chemical Society
Published on Web 01/31/2004

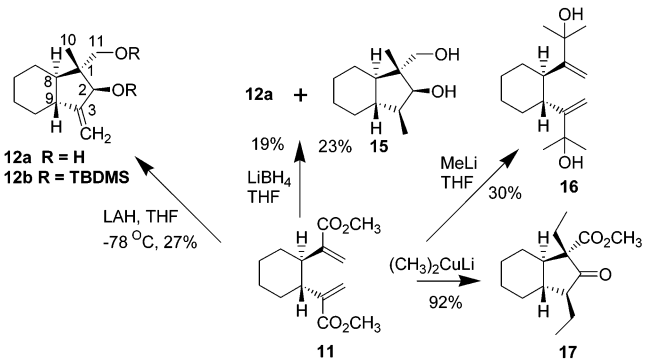
SCHEME 1. Mechanism for the LAH Reduction of 11 Amide in a Michael Reaction



ing **11** is trans. This trans structure can be rationalized by the formation and isolation of the monocyclic intermediate **10**, which underwent a Cope rearrangement to afford the *trans*-1,2-cyclohexanebis-α-acrylic acid dimethyl ester **11**. The trans stereochemistry was fully confirmed by a single-crystal X-ray structure analysis of a reaction product **12a** derived from **11**.

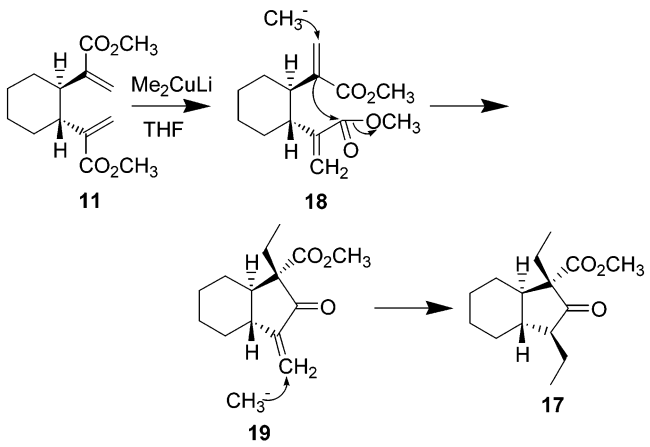
It is interesting to note that while *cis*,*syn*,*cis*-**8** is unstable at room temperature, the cis,anti,cis isomer **9** is stable even in DMF at reflux (153 °C) overnight. An attempt to use SmI_2 to open the bicyclo[2.2.0]hexane system failed to produce a new cyclohexane ring.

When the 1,2-bisacrylate **11** was treated with LAH, an unusual stereoselective, intramolecular reductive cyclization occurred to yield the *trans*-indane diol **12a**. The structure and stereochemistry of **12a** was first determined by NMR and later confirmed by X-ray analysis (Figure 1). NOE was observed between the hydrogen on C-9 and C-10 but not C-11 indicating they are cis to each other. The other bridgehead hydrogen on C-8 showed NOE with the hydrogen on C-11 again indicating they are cis. An NOE was observed between H-2 and H-11, confirming that they are cis to each other. For a full spectroscopic analysis see the Supporting Information.



The probable mechanism for this unusual reaction is outlined in Scheme 1. 1,2-Reduction of the ester carbonyl by LAH results in the formation of an oxygen−aluminum bond. This complex **13** then directs the next hydride to attack at the β position of the unsaturated ester resulting in the formation of an α carbanion. This carbanion then attacks the second ester carbonyl with the resulting loss of the methoxy group and the formation of a transitory

SCHEME 2. Mechanism for the Me_2CuLi Addition to 11



five-membered-ring ketone **14**. The aluminum directs another hydride to reduce the ketone to afford a new alcohol **12a**, whose stereochemistry is trans to the aluminate complex. Support for this mechanism can be found in the LAH reduction of a series of *N*,*N*-disubstituted α,β-unsaturated amides leading to coupling and polymerization products.[8] The reaction was explained by LAH reducing the amide carbonyl and then the oxygen−aluminum bond directing the next hydride to the β-position of the unsaturated amide, generating an α carbanion that adds to a second unsaturated amide in a Michael reaction.

When the 1,2-bisacrylate **11** was treated with sodium borohydride even in refluxing THF, no reaction was observed. However, when lithium borohydride was used, the unsaturated diol **12a** was formed together with the saturated diol **15**. Palladium-catalyzed hydrogenation of **12a** yielded **15**, thereby establishing its structure and stereochemistry at all carbons except for the new methyl group. This was determined by NOESY. A correlation was observed between the hydrogen on C-3 and the hydrogens of the hydroxymethyl group C-11, showing they are cis to each other. Thus the $LiBH_4$ reduction resulted in a highly stereoselective, intramolecular reaction similar to that of LAH.

When the 1,2-bisacrylate **11** was treated with the hard nucleophile methyllithium, both esters were reduced to the corresponding tertiary alcohols **16**. No intramolecular reactions were observed due to attack on the carbonyl carbon. However, when the 1,2-bisacrylate **11** was treated with the soft nucleophile, lithium dimethylcuprate, an intramolecular reaction resulted in the formation of the ketoester **17** in 92% yield. The probable mechanism for the lithium dimethylcuprate addition to **11** is outlined in Scheme 2, and is similar to that in Scheme 1. The soft methyl group added to the unsaturated ester **18** in a Michael reaction to yield the α-carbanion, which added to the carbonyl of the second ester to give an unsaturated ketone **19**. A second Michael reaction on the resulting unsaturated ketone **19** afforded the ketoester **17**. When only 1 equiv of lithium dimethylcuprate was used, only the final ketoester **17** and starting material **11** were isolated in approximately equal amounts, indicating that

(8) Snyder, H. R.; Putnam, R. E. *J. Am. Chem. Soc.* **1954**, *76*, 1893.

the Michael addition to the intermediate enone **19** was much faster than that to the unsaturated ester **11**. This reaction may be described as an organocopper-initiated tandem Michael addition−Dieckmann condensation reaction.[9]

Since acrylates form useful polymers, the chemistry of the novel structure **11** was investigated. Lithium in ammonia treatment of **11** afforded a polymeric solid. It was insoluble and unswellable in any solvent indicating it is probably highly cross-linked. The Raman spectrum shows it has hydroxyl absorption but no carbonyl absorption. When the proton donor, ethanol, was added to the lithium and ammonia, the polymer propagation was probably interrupted and a complex mixture of small molecules was produced.

In summary, the photocycloaddition of dimethyl cyclobut-1-ene-1,2-dicarboxylate (**1**) affords a convenient method for the synthesis of a *trans*-1,2-bisacrylate functionality. The close proximity of the two electrophilic acrylate functions, when reacted with a variety of nucleophiles, affords new methods for the intramolecular, stereoselective syntheses of a number of highly functionalized saturated indane structures.

Experimental Section

***trans*-1,2-Cyclohexanebis-α-acrylic Acid Dimethyl Ester (11).** A solution of **1** (750 mg, 4.4 mmol) dissolved in 11 mL of **7** at 0 °C was irradiated with a 450-W Hanovia UV lamp in a Dewar flask for 2.5 h. The reaction was monitored by TLC, which showed that **1** had all reacted. The solvent was evaporated and the crude product was dissolved in 30 mL of $CHCl_3$ and refluxed for 3 h. Evaporation of the solvent and flash chromatography (1:40 EtOAc−toluene) gave **11** (480 mg) at R_f ~0.3, yield 44%. IR (film) 1720, 1627. ^{1}H NMR (400 MHz) δ 1.20 (m, 2H), 1.28 (m, 2H), 1.69 (m, 2H), 1.82 (m, 2H), 2.70 (m, 2H), 3.65 (s, 6H), 5.43 (s, 2H), 6.03 (s, 2H). ^{13}C NMR (100.8 MHz) δ 26.9, 35.0, 43.3, 52.2, 124.8, 144.4, 168.2. HRMS (FAB) calcd for $C_{14}H_{20}O_4$ $[M + Na]^+$ 275.1259, found 275.1273.

Tricyclo[4.4.0.0^{2,5}]decane-2,5-dicarboxylic Acid Dimethyl Ester (9). Continued elution of the above column with 1:40 EtOAc−toluene yielded a second fraction that was concentrated in vacuo to yield **9** in 28% yield. IR 1729. ^{1}H NMR (400 MHz) δ 1.22 (m, 2H), 1.52 (m, 2H), 1.57 (m, 2H), 1.67 (m, 2H), 2.18 (m, 2H), 2.50 (m, 2H), 2.63 (m, 2H), 3.65 (s, 6H). ^{13}C NMR (100.8 MHz) δ 20.6, 22.1, 29.0, 40.6, 51.6, 53.3, 173.3. HRMS (FAB) calcd for $C_{14}H_{20}O_4$ $[M + Na]^+$ 275.1259, found 275.1267. NOESY proved the anti stereochemistry.

Tricyclo[4.2.0.02,5]octane-1,2,5,6-tetracarboxylic Acid Tetramethyl Ester (6). Further elution of the above column with 1:4 EtOAc−toluene yielded the known dimer **6**[3] in 11% yield. ^{1}H NMR (400 MHz) δ 2.38 (m, 4H), 2.69 (m, 4H), 3.75 (s, 12H). ^{13}C NMR (100.8 MHz) δ 25.8, 52.3, 53.1, 171.0.

(4*Z*,10*Z*)-Dimethyl Cyclodeca-4,10-diene-1,4-dicarboxylate (10). In the above procedure for **11**, a TLC of the irradiated solution showed two spots assigned to **10** and **11**, upon visualizing with a UV lamp. After a short period of time a third spot appeared that was assigned to **10** resulting from the thermal isomerization of **8** (estimated half-life of **8** is 15 min at room temperature). Photoadduct **8** is saturated and does not have a conjugated chromophore until it opens up to the unsaturated esters **10** and **11** and is then visible with a UV lamp. After all **1** had disappeared, the solution was quickly evaporated under vacuum and loaded on a preparative TLC plate. By this time, **8** had already isomerized to **10**. The plate was run in the refrigerator at 0 °C with 1:10 EtOAc:hexane. The lower UV quenching strip with R_f ~0.35 was collected, extracted with EtOAc, and evaporated quickly in vacuo to yield **10**. NMR spectra (^{1}H, ^{13}C, DEPT, COSY, HETCOR, NOESY) were measured immediately. ^{1}H NMR (400 MHz) δ 1.24 (m, 2H), 1.93 (d, 2H), 1.97 (m, 2H), 2.32 (m, 2H), 2.83 (d, 2H), 2.91 (m, 2H), 3.71 (s, 6H), 5.12 (dd, 2H). ^{13}C NMR (100.8 MHz) δ 29.2, 31.0, 35.3, 51.3, 126.7, 151.2, 168.6.

1-Hydroxymethyl-1-methyl-3-methyleneoctahydro-1*H*-inden-2-ol (12a). To a stirred solution of bisacrylate **11** (300 mg, 1.1 mmol) in 15 mL of THF at −78 °C was injected 1 M LAH (10 mL). The mixture was stirred for 1 h and the reaction quenched by careful addition of water. The solution was acidified by adding 2 M aqueous HCl solution and diluted with 50 mL of water and extracted with EtOAc (2 × 50 mL). The organic solution was combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by flash chromatography (3:2 EtOAc−toluene) furnished **12a** (64 mg) as a white amorphous solid (27% yield). According to NMR, de was 89%. Pure **12a** was prepared by conversion to its bis-TBDMS derivative **12b**, which was isolated in pure form chromatographically (see below) and subsequently deprotected with TBAF: thus to **12b** dissolved in 0.5 mL of THF was added 0.31 mL of TBAF and the solution was stirred for a day. The solution was evaporated and chromatographed on silica gel with 1:1 EtOAc−hexanes to yield pure diol **12a**. Crystallization from EtOAc−hexanes gave prisms. Mp 127−129 °C. IR (film) 3262, 1654. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.53 (s, 3H), 1.01 (m, 2H), 1.18 (m, 3H), 1.65 (m, 1H), 1.70 (m, 2H), 1.96 (m, 2H), 3.22 (m, 2H), 4.12 (m, 1H), 4.43 (m, 1H), 4.62 (m, 1H), 4.83 (s, 1H), 4.97 (s, 1H). ^{13}C NMR (100.8 MHz, d_6-DMSO) δ 11.1, 25.6, 25.9, 26.2, 30.0, 44.3, 44.8, 46.1, 64.4, 75.5, 105.4, 156.8. HRMS (CI) calcd for $C_{12}H_{20}O_2$ $[M]^+$ 196.1463, found 196.1465.

2-*O*-(*tert*-Butyldimethylsilyl)-1-(*tert*-butyldimethylsilyloxymethyl)-1-methyl-3-methylene-hexahydroindene Bisether (12b). To a stirred solution of crude **12a** (15 mg) in CH_2Cl_2 (0.3 mL) was added 0.036 mL of lutidine followed by 0.07 mL of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf). The mixture was stirred for 3 h and evaporated to dryness under vacuum. Chromatography on silica gel and elution with hexanes afforded the bis-TBDMS ether **12b**. Mp 54−56 °C. IR 2954, 2928, 2888, 2856, 1661 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.60 (s, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 1.01−1.30 (m, 5H), 1.60 (m, 1H), 1.77 (m, 2H), 2.04 (m, 2H), 3.31 (d, 1H), 3.37(d, 1H), 4.45 (d, 1H), 4.90 (s, 1H), 4.99 (s, 1H). ^{13}C NMR (100.8 MHz, $CDCl_3$) δ −5.3, −4.9, −4.0, −3.6, 11.5, 18.6, 18.7, 26.2, 26.3, 26.4, 26.9, 27.1, 31.1, 44.8, 45.1, 47.5, 64.8, 76.7, 106.2, 157.3. HRMS (CI) calcd for $C_{24}H_{29}O_2Si_2$ $[M + H]^+$ 425.3271, found 425. 3255.

1-Hydroxymethyl-1,3-dimethyloctahydro-1*H*-inden-2-ol (15). To a stirred solution of **11** (100 mg, 0.4 mmol) in THF (1.0 mL) at reflux was injected 2 M $LiBH_4$ in THF (1 mL) and the solution was refluxed for 4 h. Then the reaction was cooled and quenched with 2 N HCl, extracted with EtOAc (2 × 30 mL), and dried over anhydrous Na_2SO_4. Evaporation of solvent and column chromatography (1:1 EtOAc−toluene) afforded 33 mg of a mixture of **12a** and **15** at R_f ~0.3. NMR showed a mixture of 15 mg of **12a** and 18 mg of **15**, corresponding to a yield of 19% (de 93%) and 23% (de 87%), respectively. Flash chromatography (1:1 EtOAc−hexanes) through $AgNO_3$ treated silica gel separated these two compounds. For **15**: IR 3391. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.62 (s, 3H), 0.82 (d, 3H), 0.82 (m, 1H), 0.99 (m, 3H), 1.10 (m, 2H), 1.33 (m, 1H), 1.56 (m, 1H), 1.68 (m, 2H), 1.79 (m, 1H), 3.13 (m, 2H), 3.73 (dd, 1H), 3.96 (d, 1H), 4.39 (t, 1H). ^{13}C NMR (100.8 MHz, d_6-DMSO) δ 13.2, 14.2, 26.4, 26.8, 26.8, 31.2, 42.8, 48.0, 48.0, 48.7, 68.3, 75.7. HRMS (FAB) calcd for $C_{12}H_{22}O_2$ $[M + Na]^+$ 221.1518, found 221.1515.

3-[2^1-(2-Hydroxy-2-methyl-1-methylene-propyl)cyclohexyl]-2-methylbut-3-en-2-ol (16). To a stirred solution of **11** (164 mg, 0.64 mmol) in ether (7.5 mL) at room temperature was injected 1.4 M CH_3Li (4.6 mL). The solution was stirred for 1 day and then quenched with water. The solution was extracted with ether (2 × 30 mL) and the ether solution dried over anhydrous Na_2SO_4. Evaporation of solvent and flash chromatography (1:1 EtOAc−toluene) furnished **16** (50 mg): Yield 30%. R_f ~0.3. IR 3402, 1634. ^{1}H NMR (400 MHz) δ 1.25 (s, 6H), 1.31

(9) For a review of similar reactions see: Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992; Chapter 5.

(s, 6H), 1.20−1.34 (m, 4H), 1.72 (m, 2H), 1.91 (m, 2H), 2.41 (m, 2H), 4.97 (s, 2H), 5.18 (s, 2H). ^{13}C NMR (100.8 MHz) δ 27.3, 30.0, 38.8, 44.4, 72.9, 109.6, 162.3. HRMS (FAB) calcd for $C_{16}H_{28}O_2$ $[M + Na]^+$ 275.1987, found 275.1986.

1,3-Diethyl-2-oxo-octahydroindene-1-carboxylic Acid Methyl Ester (17). To a stirred suspension of CuI (114 mg, 0.6 mmol) in ether (1 mL) at 0 °C was injected 1.4 M CH_3Li (0.85 mL). The solution was stirred for 5 min and cooled to −40 °C. **11** (50 mg, 0.2 mmol) in 0.5 mLof ether was injected over a 2-min period and the solution was stirred for 1 h. The solution was quenched with NH_4Cl solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to yield **17** in 92% yield. IR 1745, 1730. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.81 (t, 3H), 0.82 (t, 3H), 1.16 (m, 1H), 1.28 (m, 3H), 1.45 (m, 1H), 1.52 (m, 3H), 1.59 (m, 1H), 1.77 (m, 3H), 1.92 (m, 3H), 3.60 (s, 3H). ^{13}C NMR (100.8 MHz, d_6-DMSO) δ 9.6, 11.2, 19.9, 21.1, 25.6, 25.8, 26.2, 31.4, 42.0, 50.5, 52.4, 56.1, 61.8, 172.4, 214.7. HRMS (FAB) calcd for $C_{15}H_{24}O_3$ $[M + Na]^+$ 275.1623, found 275.1609.

Dissolving Metal Reduction of 11. (a) Polymer. To a stirred solution of Li wire (0.2 g) in liquid ammonia (approximately 30 mL) at −78 °C was injected **11** (100 mg, 0.4 mmol) in THF (1 mL). After 3 h, NH_3 was evaporated and it gave a tightly clung black coating on the stirrer. The coating was not soluble or swellable in any common solvents. The film was suggested to be a highly cross-linked polymer. A Raman spectrum shows strong absorptions for hydroxyl but not for carbonyl, indicating that the product is a cross-linked polyalcohol. Raman: 2900−3300 (OH).

(b) Small Molecules. To a stirred solution of Li wire (0.2 g) in ether (5 mL), ethanol (8 mL), and liquid ammonia (approximately 30 mL) at −78 °C was injected **11** (50 mg, 0.2 mmol) in THF (1 mL). After 4 h, the reaction was quenched with solid NH_4Cl and the NH_3 evaporated. TLC showed that the product was a mixture of small molecules. The major single spot at R_f 0.3 in EtOAc was isolated by preparative TLC. It was a mixture of alcohols, probably different diastereomers.

Acknowledgment. Financial support for this research was provided by the National Institutes of Health, the Temple University Research Incentive Fund, Incyte, Bristol-Myers Squibb, and Wyeth-Ayerst. We thank Dr. Patrick Carroll of the University of Pennsylvania for the X-ray analysis of the diol **12a**, Dr. Jeffrey Honovich of Drexel University for the high-resolution mass spectra, Dr. Feng Qiu for NMR guidance, and Ms. Hongfei Yue for help with the chiral HPLC.

Supporting Information Available: Spectral data are available for compounds **9**, **10**, **11**, **12a**, **12b**, **15**, **16**, and **17**, and single-crystal X-ray data for **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035281I