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ASYMMETRIC SYNTHESES OF α,α,γ-TRISUBSTITUTED-γ-BUTYROLACTONES AND 2,2,3-TRISUBSTITUTED GLUTARIC ACID DERIVATIVES FROM CHIRAL BENZAMIDES

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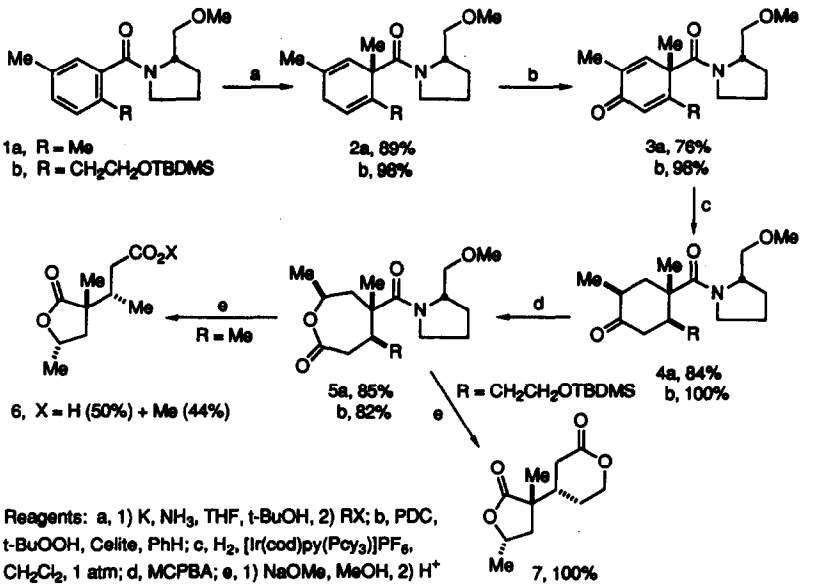
Abstract: The enantioselective conversion of aromatic carboxylic acids to acyclic structural units containing three stereogenic centers is described.

Progress in the development of methods for the asymmetric synthesis of acyclic structural units has depended to a great extent on the discovery of highly diastereoselective reactions of chiral acyclic enolates.[1] Enantiomerically pure cyclohexane derivatives are available from stereoselective alkylations and protonations of enolates derived from chiral benzamides by alkali metal in ammonia reduction.[2] Herein, we report chemistry that provides a practical "asymmetric linkage" between aromatic carboxylic acids and chiral acyclic structures; disconnection of the six-membered ring is accomplished by a regioselective Baeyer-Villiger oxidation of an intermediate 2,4,4,5-tetrasubstituted cyclohexan-1-one.[3] In particular, we report asymmetric syntheses of 2,2,3-trisubstituted glutaric acid derivatives conveniently obtained in the form of α,α,γ-trisubstituted-γ-butyrolactones.[4,5] It is noteworthy that a quaternary carbon atom[6] at the α-position of the γ-butyrolactone is obtained and that γ-butyrolactones have found extensive use in asymmetric organic synthesis.[7]

Birch reduction of the 2,5-dimethylbenzamide **1a**[8] followed by enolate alkylation with methyl iodide gave the 1,4-diene **2a** (Scheme I; isolated yields are indicated).[9] Bis-allylic oxidation of **2a** gave **3a**, which was efficiently converted to a single cyclohexanone **4a** by amide directed hydrogenation[10a] with the Crabtree catalyst system.[10b] Baeyer-Villiger oxidation of **4a** with m-chloroperbenzoic acid (MCPBA) gave **5a**.

Treatment of **5a** with sodium methoxide in methanol followed by acidification gave a separable mixture of lactone carboxylic acid and ester **6** in 94% yield and released the chiral auxiliary for reutilization.[8] An X-ray diffraction study of the highly crystalline carboxylic acid **6** (mp

Scheme I



109-110 °C) provided the molecular structure shown in Figure 1. An analogous series of conversions starting with **1b** gave the crystalline bis-lactone **7** (mp 68-70 °C).[11] Configurations of the methine carbon atoms in **7** are reasonably assigned on the basis of analogy with **6**. Furthermore, ^{1}H NMR resonances for the methyl substituents and the methine proton on the γ-lactone ring in **6** (X = H) and **7** are virtually identical, suggesting that, as with **4a**, epimerization at C(2) did not occur during preparation and isolation of **4b**.

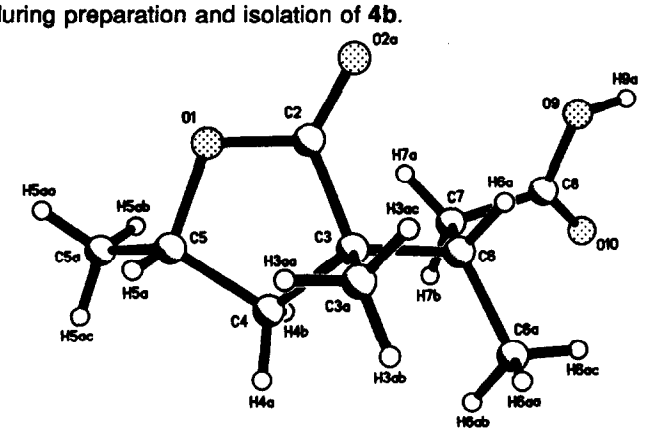
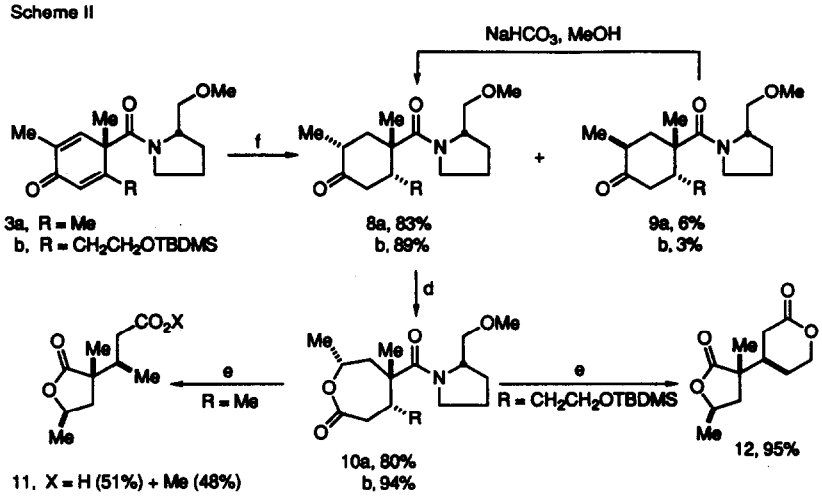


Figure 1. Molecular structure of 6 (X = H)

By utilization of a complementary hydrogenation procedure, **3a** and **3b** were converted to diastereomers of **6** and **7** (Scheme II). Hydrogenation of **3a** with 5% rhodium on alumina gave a mixture **8a** and **9a**. The minor isomer **9a** could be converted to a 9:1 mixture of **8a** and **9a** by

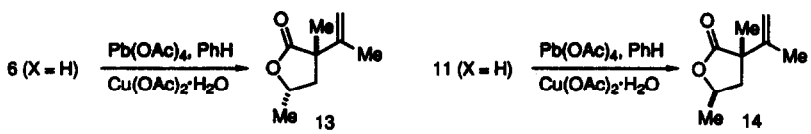
epimerization with $NaHCO_3$ in methanol. Peracid oxidation of **8a** gave **10a**, which was converted to butyrolactone **11** as described for the transformation of **5a** into **6**. The bis-lactone **12** (mp 82-84 °C) was obtained from **3b** as indicated (Scheme II).

Scheme II



Reagents: d, MCPBA; e, 1) NaOMe, MeOH, 2) H^+; f, H_2, Rh on Al_2O_3, EtOAc, 55 psi

Because ^1H NMR spectra of cyclohexanones **8a** and **9a** are characteristically different from that of **4a**, it was clear that C(5) of both **8a** and **9a** have the indicated (*R*)-configuration; however, configuration at C(2) could not be established beyond doubt. We decided to interrelate lactone-carboxylic acids **6** and **11** by way of chemical transformations. Oxidative decarboxylation[12] of **6** provided the expected lactone-olefin **13**; **11** gave a decidedly different substance, which must be formulated as **14** on the basis of ^1H, ^{13}C, IR and mass spectroscopic comparisons with **13**.



The chemistry described in this note illustrates an efficient complement to existing methods for asymmetric synthesis of acyclic structural units.[1] Latent 1,4-, 1,5- and 1,6-diol relationships are present in structures **6**, **7**, **11** and **12** and a wide range of alkyl substitution will be available by variation of alkylation reagents in previously described procedures.[2,9] Selective access to one of the glutaric acid carboxyl groups is demonstrated by oxidative decarboxylations **6** → **13** and **11** → **14**.

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8. Benzamide **1a** was prepared by acylation of (*S*)-(+)-2-(methoxymethyl)pyrrolidine with 2,5-dimethylbenzoyl chloride; **1b** was prepared by reaction of the lithium amide of the chiral auxiliary with 3,4-dihydro-7-methylisocoumarin followed by in situ O-silylation with *t*-butyldimethylsilyl (TBDMS) chloride. Satisfactory combustion analyses were obtained for all compounds reported herein except **1a**, **9b**, **6** (X = H), **13** and **14**.
9. The diastereoselectivities for reductive alkylations of **1a** and **1b** were estimated to be >50:1; for a study of the diastereoselectivity of reductive alkylation of similar substrates, see: Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931.
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11. Bis-lactones were assigned as **7** and **12** rather than ring-fused δε-lactones on the basis of FT-IR and ^{13}C NMR spectroscopic analyses.
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