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2-Methyl-(1*Z*,3*E*)-butadiene-1,3,4-tricarboxylic Acid, "Isoprenetricarboxylic Acid"

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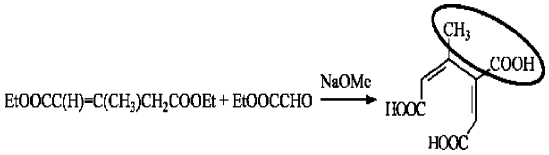
Received April 18, 2005



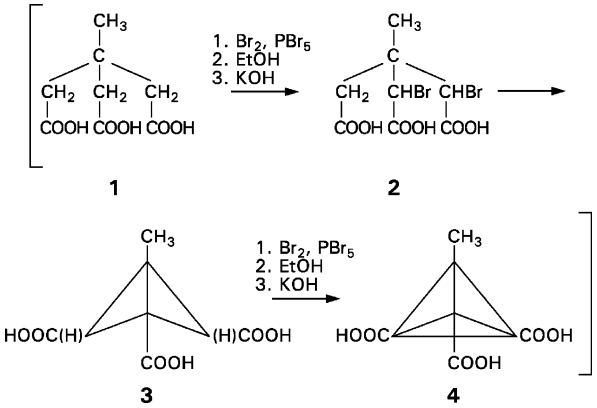
The synthesis of the title compound **7** from ethyl glyoxylate and dimethyl and diethyl β-methylglutaconate is described along with its physical properties that suggest its inability to assume a *cis*-dienoid structure due to steric hindrance between the methyl and carboxyl groups.

In the late 1940s, Professor Robert B. Woodward was concerned with possible synthetic approaches to tetrahedrane, a compound still awaiting synthesis although its tetrakis *tert*-butyl derivative has been prepared.[1]

At that time, the structures of the cage compound **4** (Scheme 1) reported by Beesley and Thorpe[2] appeared to contain this ring system,and Woodward assigned one of his students (Harold O. Larson) to attempt repetition of its synthesis (**1** > **4**, in brackets). However, Professor Woodward clearly doubted the validity of the intermediate **3**. In its place, he postulated[3] that alkali fusion of **2** had first led to a bromocyclopropane intermediate that then lost the second bromine, rearranging to form three isomeric acids of 2-methyl-1,3-butadiene-1,3,4-tricarboxylic acid (7, Scheme 2), referred to at the time as "isoprenetricarboxylic acid", following earlier nomenclature.[4a,b]

The geometrical isomers of **7** were expected to have properties consistent with those described for the three isolated isomers of **3,** and so he assigned a second student, one of us (M.B.G.), to attempt a more straightforward synthesis of at least one of these compounds. This synthesis was finally accomplished[3] through the strong base-catalyzed reaction of diethyl β-methylglutaconate **(5)** and ethyl glyoxylate **(6)** (Scheme 2). On the other hand, many attempts by Larson to repeat the Beesly and Thorpe work which depended on the preparation and alkaline fusion of the dibromination product of

SCHEME 1



the ethyl ester of ethane-1,1,1-triacetic acid (**2**) were not successful,[5] nor did any of the reaction products bear any similarity to synthetic tricarboxylic acid **7**, and the pursuit of **4** by this route was abandoned. Interestingly, however, **7** failed to exhibit the typical *cis*-dienoid ultraviolet absorption seen in, for example, *cis*,*cis*-β-methylmuconic acid **(10)**[3] obtained by the peracid oxidation of *p*-cresol.[6] Examination of Fisher−Taylor−Hirschfelder models strongly suggested that steric repulsion of the 2-methyl and 3-carboxyl groups was responsible (see **7b** below), but Professor Woodward was uneasy about this explanation. To clarify this matter, and in view of the more recent work on the stereochemistry of the lactonization of **10**,[7a,b] we have repeated the preparation of **7** and determined its properties using modern techniques, ultimately reaffirming its structure as reported in the M.B.G. thesis.

First attempts to prepare **7** depended on ring-opening reactions of the type used successfully by Pauly et al. in the conversion of 3-nitro-*p*-cresol to *cis*,*cis*-β-methylmuconic acid **(10)** with sulfuric acid[4b] or peracetic acid ring opening as described by Böeseken and Metz.[9] This would provide the advantage of ensuring fixed stereochemistry of the double bonds. However, when the peracid reaction was applied to 2-methyl-3-hydroxybenzoic acid (cresotinic acid), or even 2-methyl-3,4-dihydroxybenzoic acid, no such product was obtained, likely due to the deactivating effect of their carboxyl groups. Many other approaches were also attempted, and the reader is referred to the original thesis[3] for details.

Attention was then turned to base-catalyzed condensation reactions of glutaconic esters and aldehydes first discussed by Feist andBeyer.[10] Thus, diethyl (or here, dimethyl) β-methylglutaconate (**5**) was treated with ethyl glyoxylate (**6**) in methanolic KOH to produce an ether-extractable, somewhat unstable acid (Scheme 2). There

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(8) Cawley, J. D. *J. Chem. Soc.* **1955**, *77*, 4125.
(9) Böeseken, J.; Metz, C. F. *Rec. Trav. Chim. Pays-Bas Belg.* **1935**, *54*, 345.
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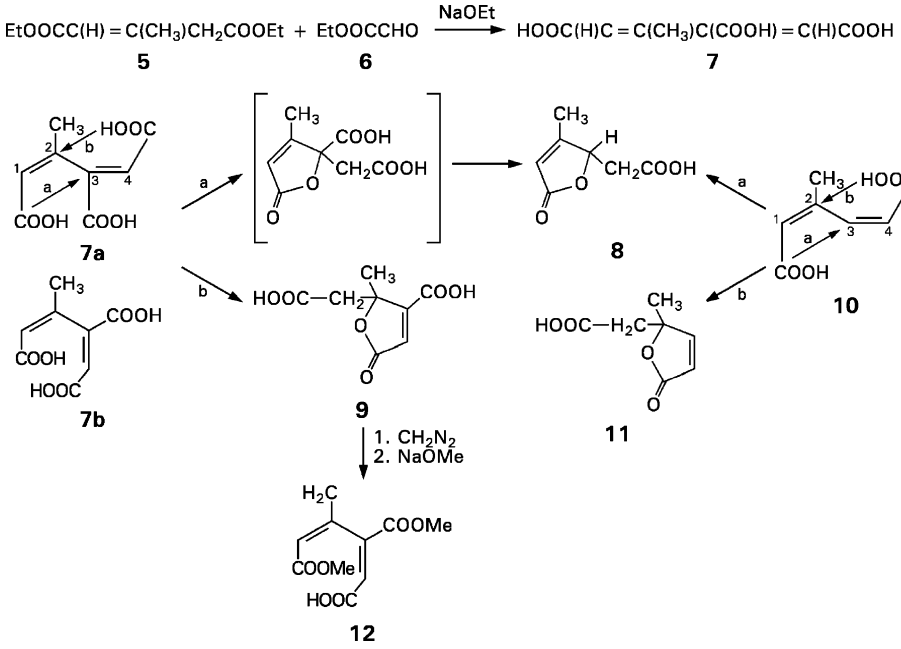
10.1021/jo0507892 CCC: $30.25
Published on Web 08/10/2005

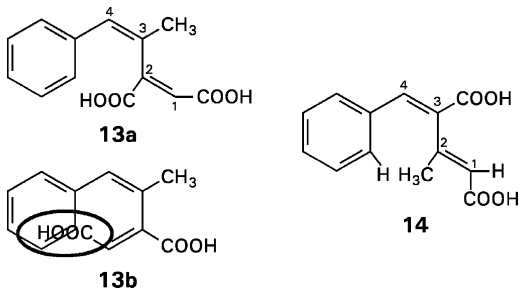
SCHEME 2



seems little doubt that this is in fact the desired "isoprenetricarboxylic acid" **7** since it has the correct molecular weight by negative-ion electrospray, losing successively three molecules of CO_2 on MS/MS, and exhibits a reasonable NMR (see below). On standing open to the atmosphere, the dry acid decomposed with evolution of gas (CO_2) in a matter of days, or more rapidly on heating in solution, to yield a product from which two lactones could be isolated by trituration with ether. The least soluble is the decarboxylation product, lactone **8**, first described by Pauly et al.,[4a] and as described in the M.B.G. thesis, it was found to be identical with a sample of authentic **8**. The second, more soluble product is the dicarboxylic acid lactone **9**. Again, both of these lactones show NMR and mass spectra that are in accord with their proposed structures and recall the very similar lactonization found to occur stereospecifically by Kirby et al. when 3-methyl-*cis*,*cis*-muconic acid **(10)** is produced in the presence of certain bacteria and fungi[7a,b] where these workers were also able to isolate lactone **11**, closely related to **9**.

The 1*Z*,3*E* orientation of the double bonds suggested by its NMR and shown in **7a** receives considerable support from the easy formation of these lactones, i.e., the 1*Z* linkage remains in **8** after decarboxylation while the 3*E* is apparent in **9**. Thus, the C_1 proton is differentiated from the C_4 proton by the presence of allylic coupling to the methyl group in the latter, and its chemical shift at δ 6.61 in both the acid and its methyl ester suggests that it is deshielded by the adjacent *cis* carboxyl at C_2 in the 1*E* conformation.[11] As expected for the 3*Z* conformation, the C_2 methyl group does not appear to be similarly deshielded at δ 2.05, but the chemical shift range available in ref 8 is too wide to be convincing. Similarly, allylic coupling constants between the H and CH_3 groups were found to be virtually identical in that reference (1.60 Hz).[11]

SCHEME 3



The apparent UV maximum of acid **7a** is at 210 nm (ϵ 15 900) like fumaric and crotonic acids rather than 265 nm (ϵ 17 800) like *cis*,*cis*-β-methyl muconic acid **10**,[6] or muconic acid (265 nm, 25 100) or *cis,cis*-β-carboxymuconic acid[12] (254 nm, 8200). This shows that there is, in fact, considerable steric hindrance between the 2-methyl and 3-carboxy groups that prevents the double bonds from attaining coplanarity in the *cis*-dienoid form **8a** responsible for absorption at that wavelength. The dimethyl ester of lactone **9** could be easily opened with sodium methoxide,[3] and the resulting dimethyl ester acid **12** apparently retains the same stereochemistry as **7** since it also shows a UV maximum at only 210 nm (ϵ 15 900).

To further examine this matter, 3-methyl-4-phenylbutadiene-1,2-dicarboxylic acid (benzal-β-methylglutaconic acid) (**13a**,**b**, Scheme 3), reported earlier by Feist and Beyer,[10] was prepared by strong base-catalyzed condensation of benzaldehyde and diethyl β-methylglutaconate.[3] Based on the known *cis* orientation of the aryl and R groups obtained in these condensations as found by Cawley,[8] **13** was expected to have the 1*E*,3*Z* stereochemistry shown in **13a** and **13b**. In this case, the *cis*-dienoid rotamer **13b** is hindered both by the interaction of the C_3 methyl and the C_2 carboxyl mentioned above, and

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more seriously by the C_1 carboxyl and the benzene ring. However, even the *trans*-dienoid form **13a** is subject to hindrance from the C_2 carboxyl and the benzene ring, preventing full planarity of the ring and *trans*-diene. In fact, **13** showed only the two maxima at 220 nm(ϵ 17 800) and 274 nm (ϵ 15 900) expected for *trans*-cinnamic acid. (204−215 nm (ϵ 15 160) and 273 nm (ϵ 20 000).[3] Similarly, Cawley working on the chemistry of vitamin A,[8] found that 2-methyl-4-phenyl-(1*E*,3*E*)-butadiene-1,3-dicarboxylic acid (**14**)[13] shown in its *trans*-dienoid form showed only *trans*-cinnamic acid absorption (276 nm, ϵ 17 600) rather than that expected for a phenylbutadiene.[13] This spectral difference was assigned to the steric hindrance between the *o*-hydrogen on the phenyl ring and the methyl group in the *trans*-dienoid rotamer **14**, an effect that might be expected to be smaller than in the case of **13a** by comparing methyl and carboxyl group sizes.

Experimental Section

The preparation of the title compound is a slight modification of that described in the M.B.G. thesis.[3] The available dimethyl ester of β-methyl glutaconic acid was used in place of the diethyl ester used in the thesis. Several other preparations, mp, and data other than NMR are also taken from the thesis.

2-Methyl-(1*E*,3*Z*)-butadiene-1,3,4-tricarboxylic acid, "Isoprenetricarboxylic acid" (7). Ten grams of dimethyl β-methylglutaconate **(5)** and 14.8 g of 50% ethyl glyoxylate **(6)** in toluene were added dropwise under nitrogen to 20 g of KOH dissolved in 150 mL of cold (0 °C) anhydrous methanol over 45 min and the reaction mixture allowed to stand overnight at room temperature. A precipitate formed in the bottom of the flask from which the original solvents were decanted, and the residue was washed with 20 mL of cold methanol. That was likewise decanted, the solid was dried under vacuum and taken up in 12 mL water, 100 mL of ether was added, and the flask was cooled in an ice bath. Concentrated HCl was added until the Congo red point was obtained, the solution was extracted with six 100 mL portions of ether, and the extracts were dried over 30 g of anhydrous sodium sulfate. The ether was evaporated at 30 °C and the residue dried with an oil pump, yielding 4.00 g of white crystals, mp 113−116 °C. This was washed with 20 mL of chloroform to remove small amounts of lactones **8** and **9** (see below) and the acid again pumped dry with an oil pump after which it melted at 130−146 °C dec with foaming. Recrystallization was quite difficult, but fine needles could be prepared by dissolving the acid in excess ether and reducing the volume. Mp: 151−152 °C. The UV shows only the low wavelength absorption expected for α,β-unsaturated acids at 214 m (ϵ 17 800).; IR (ether, cm^{-1}): ν_{max} 1709. Anal. Calcd for $C_8H_8O_6$: C, 48.01; H, 4.03. Found: C, 47.96; H, 4.25. IR (ether): 1709 cm^{-1} (COOH); 1653, 1626 cm^{-1} (C=C). ^{1}H NMR (200 MHz, THF-*d*): δ 5.75 (br s 1H), 6.61 (s, 1H), 2.04 (br s 3H). ^{13}C NMR (50.3 MHz, THF-*d*): δ 24.7, 119.7, 125.9, 148.8, 152.6, 165.6, 166.1, 166.6. IR (Nujol) (cm^{-1}) 1460, 1377. MS positive-ion electrospray in water: *m/z* 223 $(M + Na)^+$ and 239 $(M + K)^+$; negative-ion electrospray: *m/z* 199 $(M - H)^-$. MS/MS: *m/z* 155, 111, and 66 (loss of 1−3 CO_2). The acid was not particularly stable, and it is essential that it be stored under vacuum to prevent decomposition. If it is merely air-dried and placed in a bottle, pressure develops over a matter of days as the compound undergoes decarboxylation, ultimately forming lactones **8** and 9 (see below).

The trimethyl ester of **7** was prepared with ethereal diazomethane as an oil which was not crystallized but molecularly distilled at 0.3 mm. IR ($CHCl_3$, cm^{-1}): ν_{max} 1709. UV (EtOH): 214m (17 800). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.75 (br s, 1H), 6.61 (br s, 1H), 2.05 (br s, 1H), 3.78, 3.69, 3.58 (3s, 3 CH_3O). Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.51; H, 5.78. Found: C, 54.12; H, 5.73.

Lactone 8. The residue from evaporation of the above chloroform washings was triturated with ether to produce a white solid that was recrystallized from the same solvent, mp 124−126 °C either alone or on admixture with an authentic sample obtained from D. Taub prepared according to Pauly et al.[4a] Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.13. Found: C, 53.37; H, 5.17. ^{1}H NMR (200 MHz, D_2O): δ 2.05 (d, J = 1.4 Hz, 3H), 2.29 (dd, J = 9.0, 15.6 Hz 1H), 2.72 (dd, J = 15.6, 4.3 Hz, 1H), 5.24 (dd, J = 9.0, 4.3 Hz, 1H), 5.80 (dq, J = 1.4, 1.4 Hz 1H). ^{13}C NMR (50.3 MHz, D_2O): δ 14.2, 40.4, 85.0, 116.2, 173.9, 177.8. 178.0.

2-Methyl-1,3-butadiene-1,3,4-tricarboxylic Acid Monolactone (9). The ether filtrates from the above crystallization were evaporated and a few drops of methanol added. Addition of chloroform caused the lactone to precipitate and the product was recrystallized from the same solvent mixture to give polyhedra. Mp: 151−153 °C. IR ($CHCl_3$, cm^{-1}): ν_{max} 1709, 1751. Anal. Calcd for $C_8H_8O_6$: C, 48.01; H, 4.03. Found: C, 47.71; H, 3.91. Neutralization equivalent with NaOH: calcd 100.07, found 100.7.

The **dimethyl ester of 9** was prepared by treating the above monolactone with either hydrogen chloride in methanol or excess diazomethane; crystallized on trituration with ether. Mp: 44−45 °C. IR ($CHCl_3$, cm^{-1}): ν_{max} 1709, 1751. Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.28. Found: C, 52.69; H, 5.29. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62 (s 3H), 2.92, (d, J = 15.8 Hz, 1H), 3.04 (d, J = 15.8 Hz, 1H) 3.52, (s, 3H), 3.82 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.9, 40.9, 51.6, 52.6, 85.5, 126.3, 158.5, 160.9, 168.5, 169.3.

The dimethyl ester (200 mg) was allowed to stand with 23 mg of sodium dissolved in 10 mL of anhydrous methanol for 2 days, evaporated, and taken up in 5 mL of cold water. The solution was extracted once with ether, acidified, and again extracted with ether to produce the **dimethyl ester acid 12** which was recrystallized from ether. Mp: 126−128 °C. Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.28. Found: C, 52.34; H, 5.26. UV (dilute KOH): 214 m (ϵ 17 800).

Benzal β-methylglutaconic acid (13) was prepared according to ref 10 and recrystallized from aqueous ethanol. Mp: 186−192° dec. NE $C_{13}H_{12}O_4$: 117.9 (calcd 116.1). UV (dilute NaOH): ~215 m (ϵ 17 600), 274 m (ϵ 17 400) [lit.[8] UV 276 (ϵ 17 600)].

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