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Synthesis of Cyclobutanetricarboxylic Acid Derivatives via Intramolecular [2+2] Photocycloaddition

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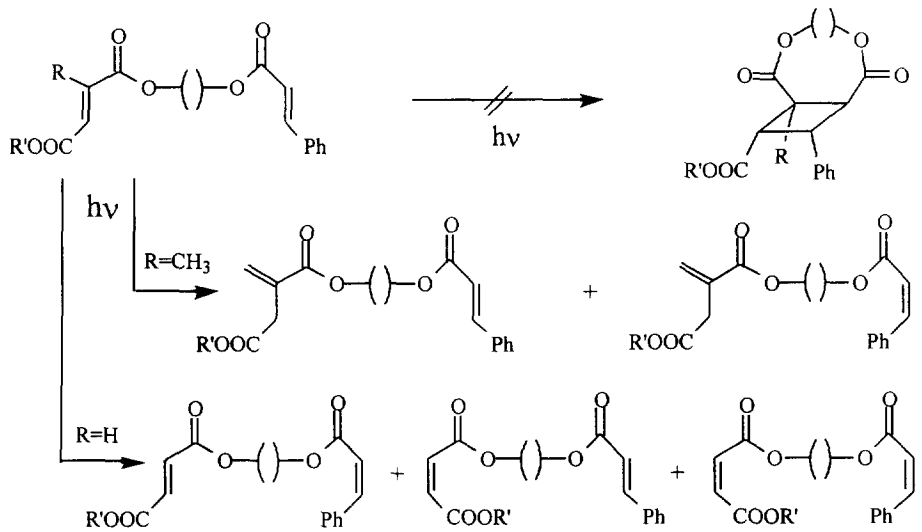
Abstract: 5-Cinnamyloxy-4-methyl-2(5H)-furanone **1** undergoes intramolecular [2+2] photocycloaddition when irradiated in acetone as solvent and sensitiser. cis/trans-Isomerization at the double bond of the cinnamyl moiety is also observed. The time dependence of the product ratio of the photolysis of **1** is reported. A photostationary equilibrium between the cyclobutanes **4** and **5** is established by irradiation of **5**. **4** (obtained in 78 % yield) is converted to the 2-methyl-4-phenylcyclobutane-1,2,3-tricarboxylic acid **7** in 73 % yield. © 1997 Elsevier Science Ltd.

Introduction

Intramolecular [2+2] photocycloaddition of cyclic α,β-unsaturated carbonyl and carboxyl compounds has been extensively applied to the synthesis of a variety of cyclobutane derivatives.[1] Derivatives of diphenylcyclobutanedicarboxylic acids can be obtained via [2+2] photodimerisation of cinnamic acid.[2,3] The resulting structures are found in tropane alkaloids (e.g. α- and β-truxiline).[4] Phenylcyclobutanetricarboxylic acids also occur as partial structure in this type of alkaloids (e.g. grahamine[5]) where the carboxylic functions are esterified with tropan-3-ol or tropan-3,6-diol. The pharmacological activity of the tropane alkaloids depends strongly on the nature of these acids.



Scheme 1: No intramolecular [2+2] cycloaddition of cinnamic ester to fumaric or mesaconic ester is observed. Instead, photodeconjugation and cis/trans isomerization take place.

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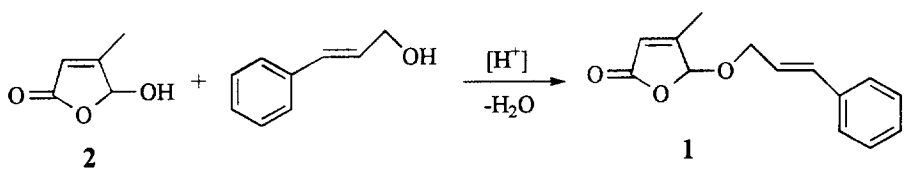
We are interested in the synthesis of phenylcyclobutanetricarboxylic acids via [2+2] photocycloaddition. Since intramolecular [2+2] cycloadditions are generally more stereoselective than the corresponding intermolecular [2+2] cycloaddition reactions, we began to study the first type of these reactions.[3,6] However, an intramolecular [2+2] photocycloaddition as it is observed for the dimerisation of cinnamic acid derivatives is not observed for cinnamic ester and mesaconic or fumaric ester (Scheme 1). (The two different ester moieties were linked by diols.) Instead, cis/trans-isomerisation of both reaction partners and photodeconjugation[7] of the mesaconic ester occurs.[8]

Results and Discussion

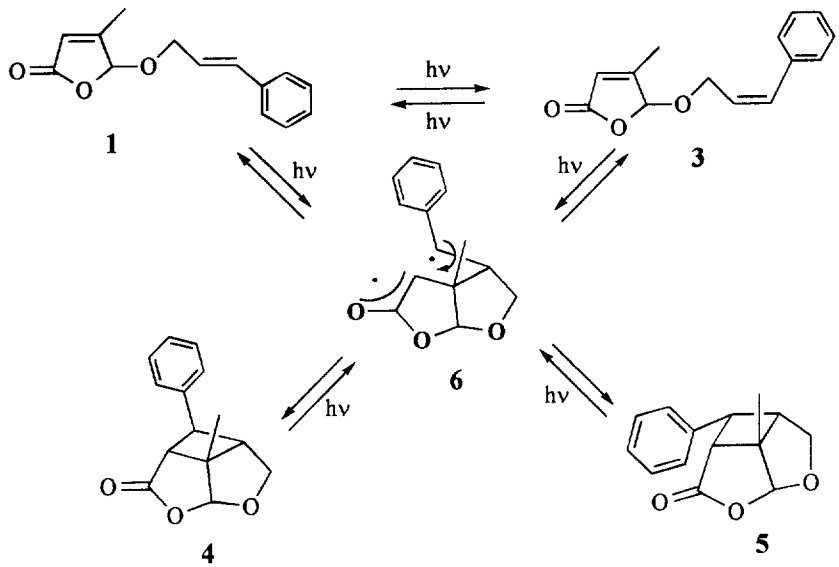
Based on this experience, we decided to study the photoreactivity of 4-methyl-5-cinnamyloxy-2(5H)-furanone **1**.[9] This compound was obtained by acetalization of 5-hydroxy-4-methyl-2(5H)-furanone **2**[10] with cinnamyl alcohol (Scheme 2). In the furanone moiety, photochemical cis/trans-isomerisation is not possible and the cinnamyl substituent is more reactive than cinnamic esters. Compound **1** was irradiated (mercury high pressure lamp Philips, HPK 125 W) at different temperatures in acetone as solvent (Scheme 3). No attempt has been made to irradiate **1** with monochromatic light because the stress was on the preparative conditions. The conversion and the ratio of the products were monitored by GC (Figures 1 - 3).



2 **1**

Scheme 2

The product ratio depends characteristically on the reaction time and the spectrum of irradiation. (The irradiations were carried out through Pyrex glass or quartz.) A photostationary equilibrium between the cis/trans-isomers **1** and **3** is rapidly established. **3** is the major isomer. The cyclobutane isomers **4** and **5** are generated by a slower reaction. Figure 1 was obtained from the irradiation in Pyrex glass. Almost only cis/trans-isomerization is observed under these conditions. Cyclobutane formation occurs when **1** is irradiated through quartz. The latter reaction is sensitised by acetone while cis/trans-isomerisation can be induced by sensitisation (triplet reaction) or direct excitation (singlet or triplet reaction). The influence of the temperature on the reaction is remarkable (compare [3g,11]). The most rapid and highest conversions are obtained at room temperature (Figure 2). The cyclobutane isomer **4** is the major product. At lower temperatures, the cyclization is slower whereas the rate of cis/trans-isomerisation remains unchanged (Figure 3). Furthermore, it can be observed that the formation of **5** is the slightly favoured way of cyclization in the beginning, while **4** becomes dominant when the reaction progresses (Figure 3, Table).



Scheme 3: Mechanism of the formation of the cyclobutanes **4** and **5** in the photochemical conversion of **1**.

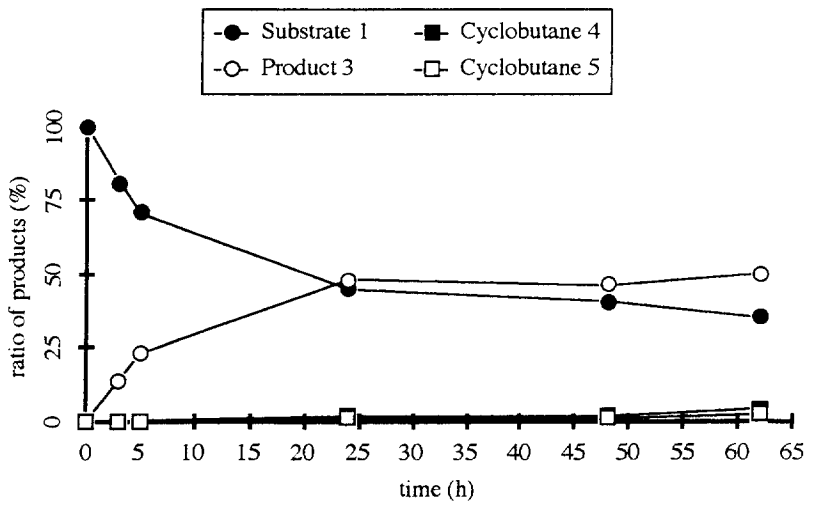


Figure 1: Irradiation of **1** in acetone at 5 °C (Pyrex).

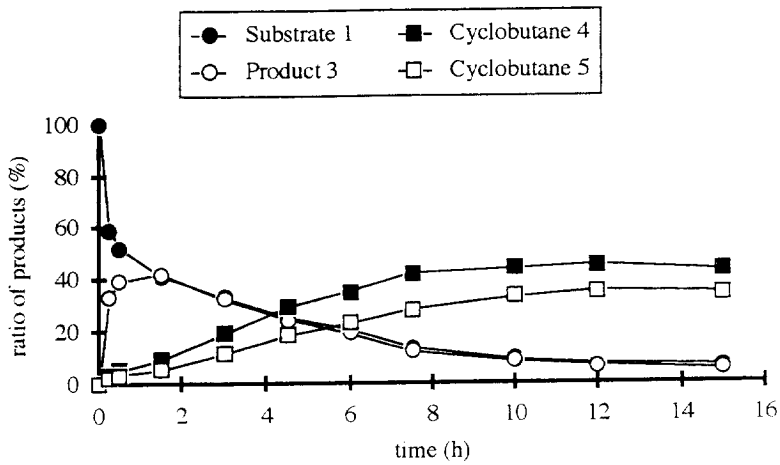


Figure 2: Irradiation of **1** in acetone at room temperature (quartz).

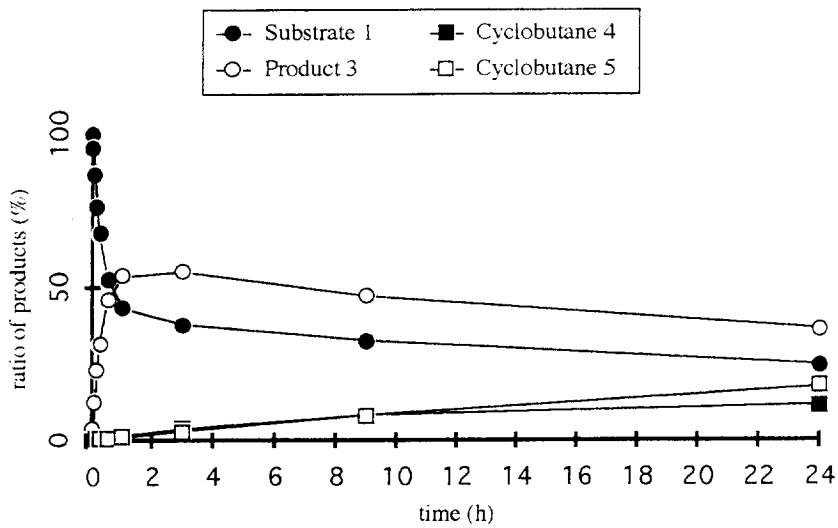


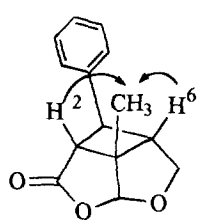
Figure 3: Irradiation of **1** in acetone at -50 °C (quartz).

Products / Conditions	1	3	4	5
Acetone/Pyrex 25 h / 5 °C	45	48	2	1
Acetone/quartz 9 h / -50 °C	32	47	8	8
Acetone/quartz 10 h / -20 °C	24	35	20	16
Acetone/quartz 10 h / -5 °C	10	19	20	28
Acetone/quartz 9 h / 10 °C	19	23	32	24
Acetone/quartz 8 h / 25 °C	13	12	42	28

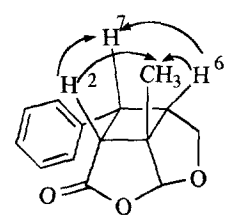
Table: Ratio of products of the photochemical reaction of **1** under different conditions.

The products **1**, **3**, **4** and **5** can be separated and purified by chromatography.

Structures of **4** and **5** were assigned by ^{1}H and ^{13}C NMR spectroscopy. In the case of compound **5**, NOE's are observed at H-7 and the methyl protons, if H-2 of H-6 are saturated (Scheme 4). In the case of **4**, a NOE is only observed for the protons of the methyl group. X-ray structural determination confirms the stereochemical assignment of **4** and **5**.[12]



4



5

Scheme 4: Structural assignment on the basis of NOE measurements.

The photostationary equilibrium is also established when the pure compound **5** is irradiated (Figure 4). In the equilibrium between the products of the cyclization and the olefinic products **1** and **3**, the cyclobutanes **4** and **5** clearly dominate. The isomerisation very likely proceeds via the intermediate **6** (Scheme 3). This intermediate rather cyclize to yield the compounds **4** and **5**, while splitting of the remaining C-C bond to yield the furanones **1** and **3** is less frequent. This type of isomerisation of cyclobutanes may also proceed via photochemically induced single electron transfer.[13] The repeated equilibration reaction was also used to transform the mixture of **1**, **2** and **5** into **4**. Due to this additional operation, **4** was obtained in a 78% yield. Isomer **5** can be obtained preferentially at lower temperature and at a low conversion.

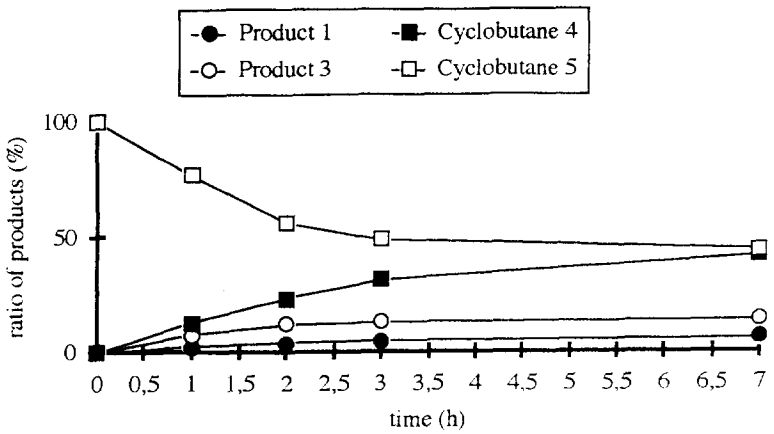
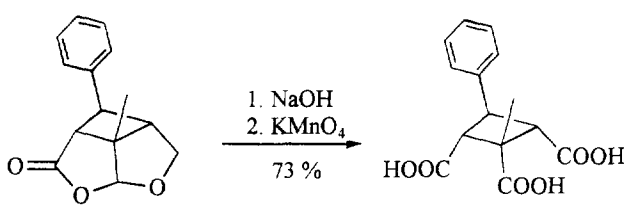


Figure 4: Cycloreversion of **4** in acetone at 10 °C (quartz).

The product ratio of the intramolecular [2+2] photocycloaddition consequently results of a series of stereorelevant elementary steps (Scheme 3). Photochemical cis/trans isomerisation at the C-C double bond of the cinnamyl moiety of **1** as well as the rotation of a C-C single bond of the 1,4-biradical intermediate **6** and the photostationary equilibrium between cyclobutanes **4** and **5** play an important role. Further on, the product ratio depends on the temperature, since each elementary step of the overall reaction is differently influenced by this reaction parameter. At the moment, a more detailed discussion of the temperature influence on the different elementary steps is not possible.

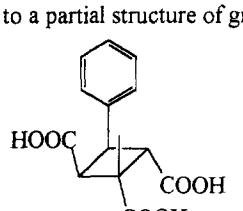
Compound **4** was transformed to the desired methylphenyltricarboxylic acid **7** as indicated in scheme 5.



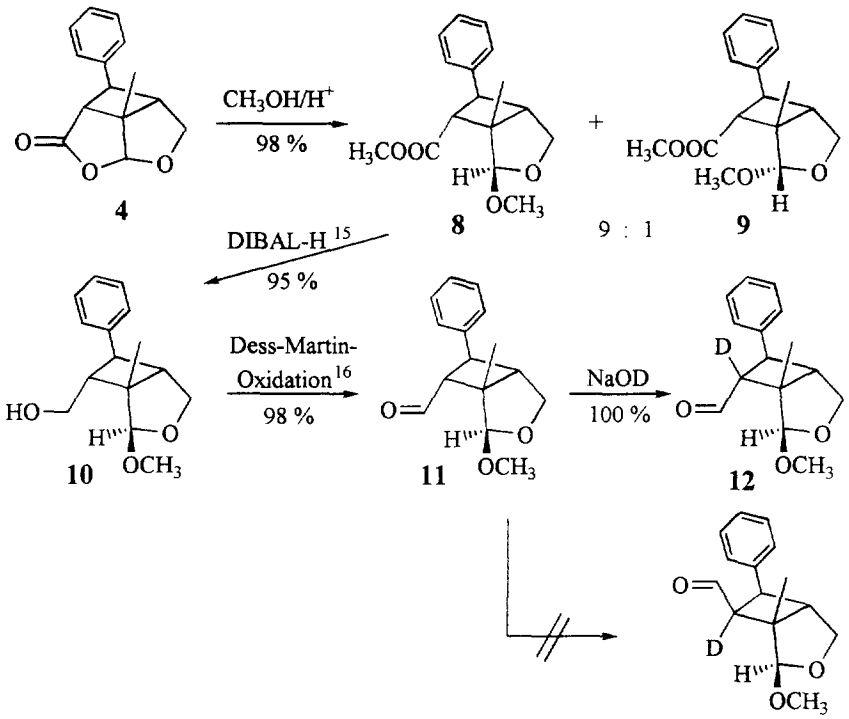
4 **7**

Scheme 5

Further on, we tried to change the configuration at the α-carbon of one carboxylic acid function.[14] The product of this transformation corresponds to a partial structure of grahamine **13**.[5]



13



Scheme 6: Transformation of **4** into the aldehyde **11** and α-deuteration of **11**. No isomerization equilibrium is observed under this reaction condition.

The cyclobutane isomer **4** was methanolized under acidic conditions. A product radio of 9/1 was found (Scheme 6) for the resulting bicyclic products **8** and **9**. The major isomer was converted to the aldehyde **11**. Treatment with NaOD afforded deuteration in the α-position of the aldehyd function without isomerisation via the intermediately generated enolate. Other methods to establish an equilibrium between the corresponding isomers which were successfully applied to similar compounds (deprotonation with triethylamine, NaOMe, NaH/THF, t-BuOK/THF, LDA/THF in the presence or absence of HMPA) failed in our case.

Conclusion

This paper reports a straightforward synthesis of a cyclobutanetricarboxylic acid in gram quantity from the bichromophoric furanone **1** of easy synthetic access. The stereoselectivity of the photochemical key step can be improved by a re-equilibration of the minor stereoisomer.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-300. TMS was used as internal standard. IR spectra: Perkin-Elmer PE 1750 FT. MS: Varian MAT 212 (70 eV). GC: Hewlett Packard 5890, Series II (Column: HP-FFAP: 25 m x 0.3 mm).

5-Cinnamyloxy-4-methyl-2(5H)-furanone **(1):** A solution of 4-methyl-5-hydroxy-2(5H)-furanone[10] (44.8 g, 0.5 mol), cinnamyl alcohol (60 g, 0.5 mol) and a catalytic amount of pTsOH was stirred under reflux for 24 hours with a water trap. The cooled mixture was washed with saturated aqueous $NaHCO_3$ solution and water. The organic phase was dried with $MgSO_4$ and evaporated. The residue was purified by chromatography (silica gel, hexane/ethyl acetate: 4/1). Recrystallisation from ether gave **1** as colourless needles (31 g, 34 %): m.p. 58 - 59°C. ^{1}H NMR (300 Mz, $CDCl_3$): δ = 2.0 (s, 3H), 4.32 (dd, 1H, J = 7, 12 Hz), 4.47 (dd, 1H, J = 6, 12 Hz), 5.71 (s, 1H), 5.82 (s, 1H), 6.27 (ddd, 1H, J = 16, 7, 6 Hz), 6.6 (d, 1H, J = 16 Hz), 7.22 - 7.4 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7, 163.7, 136.0, 134.2, 128.5, 128.3, 126.5, 123.7, 118.9, 102.8, 70.3, 13.2 ppm. IR (KBr): ν = 2920, 2870, 1790, 1770, 1660, 1130, 990, 890, 760, 740, 690 cm^{-1}. MS: *m/z* (%) = 230 (M^+, 3), 105 (10), 97 (8), 86 (39), 84 (61), 77 (4), 51 (29), 49 (100). $C_{14}H_{14}O_3$ (230.26): calcd. C 73.02, H 6.13, found C 72.83, H 6.07.

Photochemical reaction of **1**: After 30 min of thermostatisation, a solution of **1** (2 g, 8.6 mmol) in 220 ml acetone (flushed with nitrogen) was irradiated for 10 h (photoreactor fitted with an immersion well, mercury high pressure lamp Philips, HPK 125 W). The solvent was removed and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate: 3/1).

compound **3**: Yield: 0.1 g (5 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.0 (s, 3H), 4.51 (dd, 1H, J = 7, 12.5 Hz), 4.59 (dd, 1H, J = 6, 12.5 Hz), 5.70 (s, 1H), 5.85 (s, 1H), 6.27 (ddd, 1H, J = 6, 7, 16 Hz), 6.7 (d, 1H, J = 16 Hz), 7.22 - 7.40 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6, 163.4, 136.0, 134.0, 128.9, 128.7, 126.6, 123.7, 112.7, 103.4, 66.6, 13.3 ppm. $C_{14}H_{14}O_3$ (230.26): calcd. C 73.02, H 6.13, found C 73.34, H 6.20.

compound **4**: Yield: 0.7 g (35 %) as colourless needles: m.p. 116 - 117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.5 (s, 3H), 2.79 (m, 1H), 2.87 (dd, 1H, J = 4.3, 1.5 Hz), 3.27 (t, 1H, J = 4.3 Hz), 4.21 (dd, 1H, J = 8.7, 2.5 Hz), 4.35 (dd, 1H, J = 8.7, 6.7 Hz), 5.70 (s, 1H), 7.2 - 7.4 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.6, 141.5, 128.9, 127.2, 126.4, 112.7, 76.0, 50.6, 47.4, 47.1, 45.2, 18.4 ppm. IR (KBr): ν = 2850, 1770, 1460, 1380, 770, 740, 710 cm^{-1}. MS: *m/z* (%) = 230 (M^+, 20), 133 (71), 105 (100), 98 (24), 91 (17), 83 (49), 82 (33), 77 (19), 55 (14), 51 (14), 39 (18). $C_{14}H_{14}O_3$ (230.26): calcd. C 73.02, H 6.13, found C 72.29, H 6.05.

compound **5**: Yield: 0.5 g (25 %) as cubic crystals: m.p. 111 - 112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 3H), 2.98 (dddd, 1H, J = 10.3, 8.6, 6.1, 2.1 Hz), 3.24 (dd, 1H, J = 10.4, 2.1 Hz), 3.97 (dd, 1H, J = 6.1, 10.4 Hz), 4.24 (pseudo t, 1H), 4.31 (dd, 1H, J = 10.4, 8.6 Hz), 7.2 - 7.4 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.3, 136.0, 128.4, 127.6, 126.9, 111.4, 69.9, 52.0, 45.6, 44.5, 36.7, 18.3 ppm. IR (KBr): ν = 2840, 1770, 1500, 1460, 1380, 1360, 730, 720, 700 cm^{-1}. MS: *m/z* (%) = 230 (M^+, 19), 156 (16), 147 (15), 133 (44), 98 (22), 97 (17), 105 (83), 83 (75), 82 (100). $C_{14}H_{14}O_3$ (230.26): calcd. C 73.02, H 6.13, found C 73.07, H 6.04. 0.1 g (5 %) of **1** was also isolated.

Methylcyclobutanetricarboxylic acid **7:** A solution of **4** (0.5 g, 2mmol) in 50ml of a 2M NaOH solution was heated for 2h at ca 100 °C. 50 ml of an aqueous solution of $KMnO_4$ (6 %) was added to the cooled solution (0°C). The resulting mixture was kept at this temperature for 6h. It was then maintained at room temperature for 10 h. 50 ml of ethanol was added. The solution was filtered and concentrated to 100 ml. HCl was added to reach pH 3. The mixture was extracted with ether. The organic phase was dried with $MgSO_4$, filtered and evaporated to yield 7 as a white foam (0.4 g, 73 %). ^1H NMR (300 MHz, d_6-DMSO): δ = 1.49 (s, 3H), 2.99 (d, 2H, J = 10.1 Hz), 4.09 (t, 1H, J = 10.1 Hz), 7.2 - 7.4 (m, 5H), 12.5 (broad s, 3H) ppm. ^{13}C NMR (d_6-DMSO): δ = 174.1, 172.9, 142.5, 128.1, 126.8, 126.2, 50.5, 48.7, 40.1, 24.3 ppm. $C_{14}H_{14}O_6$ (278.27): calcd. C 60.43, H 5.07, found C 59.81, H 5.21.

Acid catalyzed methanolysis of **4:** A solution of **4** (1 g, 4.3 mmol) in methanol with 0.3 ml conc. H_2SO_4 was stirred 24 h at 10 °C. After removal of the major part of the solvent, the residue was dissolved in ether, washed with saturated aqueous $NaHCO_3$ and water. The organic phase was dried with $MgSO_4$ and evaporated to dryness. Chromatography of the residue (silica gel, hexane/ethyl acetate: 3/1) yielded **8** (1 g, 87 %) and **9** (0.1 g, 8 %) as a syrups.

Compound **8**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 3H), 2.50 (dd, 1H, J = 6.1, 4.0 Hz), 3.00 (d, 1H, J = 8.8 Hz), 3.35 (s, 3H), 3.55 (dd, 1H, J = 8.8, 6.1 Hz), 3.71 (s, 3H), 3.80 (d, 1H, J = 9.1 Hz), 3.88 (dd, 1H, J = 9.1, 4.0 Hz), 4.80 (s, 1H), 7.2 - 7.4 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.3, 143.4, 128.5, 126.5, 126.4, 106.0, 70.3, 54.7, 51.9, 51.6, 49.7, 48.4, 41.0, 20.5 ppm. $C_{16}H_{20}O_4$ (276.33): calcd. C 69.54, H 7.29, found C 69.56, H 7.64.

Compound **9**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3H), 2.50 (ddd, 1H, J = 3.6, 7.5, 8.2 Hz), 2.85 (d, 1H, J = 9.2 Hz), 3.30 (s, 3H), 3.66 (s, 3H), 3.68 (dd, 1H, J = 9.2, 8.2 Hz), 3.89 (dd, 1H, J = 9.0, 3.6 Hz), 4.18 (dd, 1H, J = 9.1, 7.5 Hz), 4.72 (s, 1H), 7.2 - 7.4 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.9, 143.5, 128.4, 126.5, 126.3, 110.1, 72.5, 55.3, 51.3, 51.1, 49.4, 48.3, 45.3, 24.5 ppm. $C_{16}H_{20}O_4$ (276.33): calcd. C 69.54, H 7.29, found C 69.63, H 7.53.

Reduction of **8:** To a stirred cooled (0 °C) solution of **8** (0.68 g, 2.46 mmol) in 13 ml toluene was added under argon atmosphere dropwise 15 ml (7.38 mmol) of 1 M solution of diisobutylaluminium hydride in toluene. After 2 h saturated aqueous ammonium chloride solution was added and the reaction mixture was warmed to room temperature. The phases were separated. The aqueous phase was extracted with ether. The combined organic phases were washed with water, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography of the residue (silica gel, n-hexane/ethyl acetate: 3/1) yielded **10** (0.56 g, 92 %) as an oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3H), 2.37 (m, 1H), 2.46 (apparent t, 1H, J = 4.6 Hz), 2.2 - 2.4 (broad s, 1H), 2.74 (dd, 1H, J = 7.6, 5.4 Hz), 3.36 (s, 3H), 3.76 (d, 1H, J = 8.8 Hz), 3.80 (m, 2H), 3.88 (dd, 1H, J = 8.8, 4.6 Hz), 4.92 (s, 1H), 7.16 - 7.32 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.7, 128.5, 126.6, 126.1, 105.7, 70.6, 61.7, 54.5, 50.7, 48.6, 47.1, 42.8. 20.7 ppm. IR (KBr): ν = 3400, 2870, 2830, 1150, 1100, 1030, 970, 640, 610 cm^{-1}. MS: *m/z* (%) = 248 (M^+, 3), 170 (50), 157 (52), 155 (56), 129 (39), 117 (30), 92 (34), 91 (44), 83 (100). $C_{15}H_{20}O_3$ (248.32): calcd. C 72.55, H 8.12, found C 72.51, H 8.15.

Oxidation of **10:** A solution of **10** (0.21 g, 0.85 mmol) in 5 ml methylenechloride was added to a stirred solution of periodinane (Dess Martin reagent) (0.5 g, 1.17 mmol), in methylenechloride. After 20 min, the homogeneous reaction mixture was diluted with 20 ml of ether. The resulting suspension was added to 20 ml of 1.3 M NaOH. The mixture was stirred for 10 min. The organic phase was separated and washed with 20 ml of 1.3 M NaOH and 25 ml water. Removal of ether yielded **11** (0.2 g, 96 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3H), 2.60 (t, 1H, J = 5.1 Hz), 2.96 (dd, 1H, J = 7.8, 1.7 Hz), 3.34 (s, 3H), 3.57 (dd, 1H, J = 5.4, 7.8 Hz), 3.81 (d, 1H, J = 9.1 Hz), 3.89 (dd, 1H, J = 8.8, 4.6 Hz), 4.90 (s, 1H), 7.21 - 7.35 (m, 5H), 9.86 (d, 1H, J = 1.7) ppm. ^{13}C NMR ($CDCl_3$): δ = 201.4, 143.1, 128.6, 126.5, 104.6, 70.1, 58.6, 54.5, 50.5, 48.5, 39.2, 20.5 ppm. IR (KBr): ν = 3060, 3020, 2960, 2940, 2880, 2850, 1730, 1450, 1250, 930, 750, 700 cm^{-1}. MS: *m/z* (%) = 246 (M^+, 5), 186 (29), 193 (29), 157 (34), 129 (34), 115 (34), 113 (100), 91 (30), 82 (86). $C_{15}H_{18}O_3$ (246.31): calcd. C 73.15, H 7.38, found C 73.02, H 7.47.

Deuteration of **11:** A solution containing 0.1 g (0.85 mmol) of **11** in 1.5 ml of NaOD (ca. 0.3 N) in THF was stirred for 24 h at room temperature. The solution was concentrated to dryness at room temperature under reduced pressure. The residue was washed several times with methylene chloride. The resulting solution was dried with $MgSO_4$, filtered and evaporated to yield **12** (0.1 g, 100 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3H), 2.60 (t, 1H, J = 5.1 Hz), 3.34 (s, 3H), 3.57 (d, 1H, J = 5.4 Hz), 3.81 (d, 1H, J = 9.1 Hz), 3.89 (dd, 1H, J = 8.8, 4.6 Hz), 4.90 (s, 1H), 7.21 - 7.35 (m, 5H), 9.86 (d, 1H, J = 1.7) ppm. ^{13}C NMR ($CDCl_3$): δ = 201.4, 143.1, 128.6, 126.5, 104.6, 70.1, 54.5, 50.5, 48.5, 39.2, 20.5 ppm.

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