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Cis-3,5-Dimethyl-3,5-Piperidinedicarboxylic Acid, An Amino Diacid Variant of Kemp's Triacid

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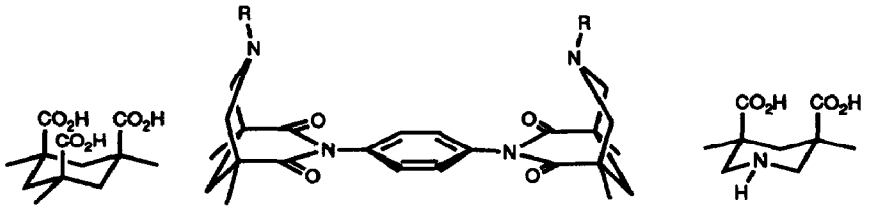
Abstract: *Cis*-3,5-dimethyl-3,5-piperidinedicarboxylic Acid (3) and several of its derivatives have been synthesized starting from 3,5-pyridinedicarboxylic acid. The ^{1}H NMR spectra indicate that these compounds assume a single conformation having the two carbonyl substituents in axial positions.

Kemp's triacid, 1,[1] has proven to be a useful template for the preparation of synthetic receptors,[1b-d,2,3] self-replicating molecules,[4] and chiral auxiliaries;[5] it has also been used in the study of stereoelectronic effects in cyclization reactions[6] and strain effects in intramolecular amide acylolysis reactions.[7] A potentially useful variation of this structure would have an amine in place of one of the carboxylic acids. One such molecule is 3, which we envision could be used to construct molecular clefts like 2 that might bind ligands possessing acidic functionalities. Toward this end *cis*-3,5-dimethyl-3,5-piperidinedicarboxylic acid (3) and several of its derivatives have been prepared.

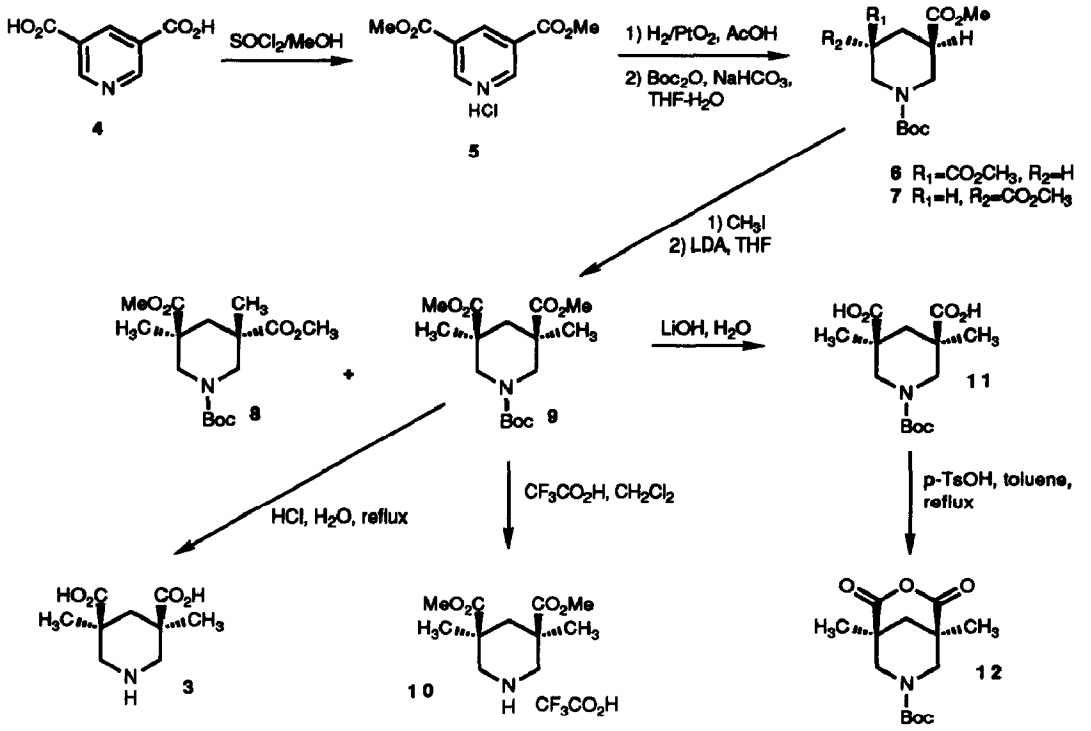


1 2 3

Outlined below in Scheme 1 is the synthetic route used to generate 3 and its derivatives. Fischer esterification of 3,5-pyridinedicarboxylic acid (4) using $SOCl_2$ and CH_3OH yields the diester 5 in nearly quantitative yield. Reduction of the pyridine ring in 5,[8] followed by acylation of the resulting amine with Boc_2O provides an approximately 1:1 mixture of *cis* (6) and *trans* (7) isomers. Although these two isomers can be readily separated by flash chromatography,[9] the following alkylation step is conveniently run using the mixture of isomers. Accordingly, addition of LDA to a THF solution of CH_3I and 6 and 7 provides two isomeric products, the desired *cis* isomer 9 and the unwanted *trans* isomer 8, in an overall yield around 70%.[10] The two isomers were identified based on the appearance of their C4 methylene in the ^{1}H NMR spectrum. In 8, the methylene hydrogens are equivalent and appear as a singlet, while in 7, the

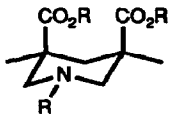
same methylene hydrogens are non-equivalent and each appears as a doublet with J=14 Hz. Although **8** is the major isomer obtained from the reaction (**8**:**9** = 4:1), workable 0.1-0.5 g amounts of the desired isomer **9** can readily be obtained following flash chromatography of the product mixture.[11] Resonances in the ^{1}H NMR spectra of **9** were assigned from the ^{1}H-COSY spectrum.

Scheme 1

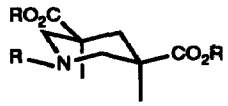


Preparation of **3** and its derivatives **10**, **11** and **12** is readily achieved starting from **9**. Simply refluxing **9** overnight in a dilute, aqueous HCl solution followed by evaporation yields **3** as a crystalline solid. The diester-amine **10** can be obtained as its trifluoroacetate salt by treating **7** with trifluoroacetic acid in CH_2Cl_2, then evaporating the solvent. Saponification of **9** with LiOH provides diacid **11** as a crystalline solid. Simply refluxing **11** in a toluene solution containing a catalytic amount of p-toluenesulfonic acid generates anhydride **12**.[12]

The two conformations available to **3**, **9**, **10** and **11** are shown below as **A** (two axial carbonyls, two equatorial methyls) and **B** (two axial methyls, two equatorial carbonyls). Analysis of the ^{1}H NMR spectra of **3**, **9**, **10**, **11** and **12** indicates that the preferred conformation for these compounds is **A**. First, the ^{1}H NMR spectra of monocyclic **3**, **9**, **10**, and **11** are very similar to that of the bicyclic anhydride, **12**, which is covalently constrained to conformation **A**. Second, as



A



B

shown in Table I, the piperidine methylene protons all exhibit large differences in chemical shift (Δδ) between the axial and equatorial positions. For the C4 methylenes, the differences in chemical shift between axial and equatorial range from 0.60 to 1.54 ppm, while for the C2, C6 methylenes the differences range from 0.81 to 2.28 ppm. Typical Δδ values between axial and

Table I. ^{1}H Chemical Shift Values for **3** and its Derivatives.

	C2, C6 methylenes			C4 methylene		
Compound	axial	equatorial	Δδ	axial	equatorial	Δδ
3	3.64	2.73	0.91	2.53	1.58	0.95
9	4.31	2.64	1.67	2.67	1.27	1.40
10	3.69	2.88	0.81	2.75	1.48	1.27
11	4.59	2.31	2.28	2.77	1.23	1.54
12	4.36	2.66	1.70	2.18	1.58	0.60

equatorial protons in conformationally mobile cyclohexanes lie between 0.6-0.8 ppm.[13] That all of the Δδ values seen with **3**, **9**, **10**, and **11** are well above this range indicates that these molecules are not in equilibrium between conformations **A** and **B**. Rather, the Δδ values support the conclusion that **3**, **9**, **10** and **11** assume only one of the two possible conformations, and given the demonstrated preference for carbonyls rather than methyls in the axial positions in Kemp's triacid and its derivatives,[1a] the preferred conformation is **A**.

Presently work is proceeding on the reaction of **12** with 1,4-phenylenediamine to produce molecular cleft **2**. Details regarding this work will be presented in due course.

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9. Representative procedure: To a solution of 5.16 g (22.3 mmol, 1 equiv) of **5** in 50 mL glacial AcOH was added 66 mg PtO_2, and the resulting suspension was hydrogenated at 50 psi for 12 h, after which the catalyst was removed by filtration through celite. Evaporation of the filtrate yielded an oil, which was then dissolved in 50 mL THF and 50 mL H_2O. To the resulting solution was then added 10.2 g (0.12 mol, 5.5 equiv) of $NaHCO_3$ and 4.87 g (22.3 mmol, 1 equiv) of Boc_2O. After stirring 2 h at 23°C the THF was evaporated. The remaining aqueous solution was extracted 3 x 75 mL CH_2Cl_2, and the combined extracts were washed with 50 mL brine, dried ($MgSO_4$), filtered and evaporated. An oil which partially crystallized was obtained. Analysis of the crude product by GC-MS indicated a 1:1 mixture of **6** and **7**. Flash chromatography (1:1 Et_2O/hexane) then afforded 1.65 g of pure **6** (25%) and 1.26 g of pure **7** (19%), along with 2.82 g of a mixture of **6** and **7** (42%). Spectral data: **6**: a white, crystalline solid, m.p. 91.0-91.5°C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.34 (2H, br s), 3.70 (6H, s), 2.71 (2H, m), 2.45 (3H, m), 1.65 (1H, m), 1.47 (9H, s). TLC, R_f 0.86 (Et_2O). Anal. Calcd. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.73; H, 7.44; N, 4.66. **7**: a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (2H, m), 3.70 (6H, s), 3.52 (2H, m), 2.82 (2H, m), 2.10 (2H, m), 1.45 (9H, s). Anal. Calcd. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.46; H, 7.48; N, 4.58.
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11. Representative procedure: To a solution of 2.82 g (9.37 mmol, 1.0 equiv) of a 1:1 mixture of **6** and **7** in anhydrous THF under N_2 was added 10 mL (0.16 mol, 17 equiv) of CH_3I, followed by dropwise addition over 15 min of 10.3 mL (20.6 mmol, 2.2 equiv) of 2.0 *M* LDA. After stirring 4 h, 4 mL of glacial AcOH was added and the solvents evaporated. The residue that remained was redissolved in 100 mL EtOAc and washed with 50 mL portions of 1.0 *M* HCl (3x), saturated $NaHCO_3$ (3x) and brine (1x). The EtOAc was dried ($MgSO_4$), filtered and evaporated to an oil. Analysis of the crude oil by GC-MS indicated a 4:1 ratio of **8**:**9**. Flash chromatography (1:3 EtOAc/hexane) then provided 1.74 g of pure **8** (56%), and 262 mg of pure **9** (8%). Spectral data for **9**: a white, crystalline solid, m.p. 68-70°C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (2H, d, J=13 Hz), 3.63 (6H, s), 2.67 (1H, d, J=14 Hz), 2.64 (2H, d, J=13 Hz), 1.49 (9H, s), 1.27 (1H, d, J=14 Hz), 1.17 (6H, s). IR ($CHCl_3$ solution) 1746, 1697 cm^{-1}. TLC, R_f 0.60 (1:1 EtOAc/hexane). Anal. Calcd. for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.58; H, 8.01; N, 4.33.
12. NMR data for derivatives. **3**: ^1H NMR (300 MHz, D_2O) δ 3.64 (2H, d, J=13 Hz), 2.73 (2H, d, J=13 Hz), 2.53 (1H, d, J=14 Hz), 1.58 (1H, d, J=14 Hz). **10**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.6 (2H, br s), 3.73 (6H, s), 3.69 (2H, d, J=12 Hz), 2.88 (2H, d, J=12 Hz), 2.75 (1H, d, J=14 Hz), 1.48 (1H, d, J=14 Hz), 1.27 (6H, s). **11**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.5 (2H, br s), 4.59 (2H, m), 2.77 (1H, d, J=14 Hz), 2.31 (2H, m), 1.23 (1H, d, J=14 Hz), 1.45 (9H, s), 1.23 (6H, s). **12**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (2H, m), 2.66 (2H, d, J=12 Hz), 2.18 (1H, d, J=14 Hz), 1.58 (1H, d, J=14 Hz), 1.42 (9H, s), 1.33 (6H, s).
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