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Twisted Amide Analogues of Tröger's Base

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In memory of Professors Manfred Hesse and Jan Sandström

Tröger's base (TB),[1] 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]-diazocine (*rac*-**1**), is a rigid chiral molecule with a concave V-shaped aromatic surface (Figure 1). These

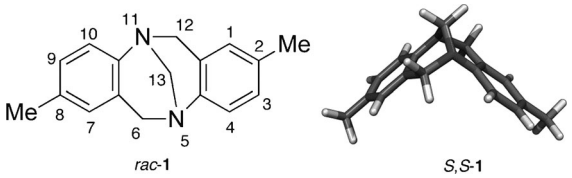
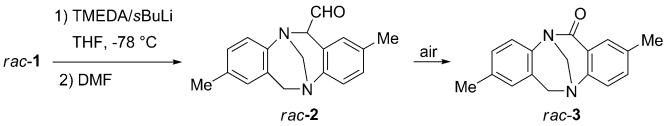


Figure 1. Tröger's base (TB) (*rac*-**1**) and 3D representation of the energy minimized structure (Merck Molecular Force Field) of the *S*,*S*-isomer of **1**.

intriguing properties have rendered TB and its analogues attractive building blocks for exploitation and application in molecular recognition, catalysis, enzyme inhibition and as torsional balances.[2–4] Although TB itself and TB analogues containing electron-rich substituents are prepared by a simple procedure,[1,5] access to other analogues has been hampered by the absence of general methodologies to functionalize the TB bicyclic diazocine core. Thus, although aryl ring functionalization is well developed,[6–10] derivatization of the diazocine ring has been limited to *N*-mono and –dialkylation,[11] cleavage and replacement of the methylene bridge,[12] and direct exchange of the methylene for other bridges by various methods.[13]

As part of our ongoing work,[6–10,14] we aimed to devise new synthetic chemistry for the functionalization of the chiral cleft of TB in order to provide new derivatives for studies in catalysis and molecular recognition. In the course of these studies, we serendipitously prepared the first TB twisted bis-amide (*rac*-**4**). The availability of **4** logically stimulated studies of its unusual structural, physical, and chemical properties, including hydrolysis to form **7**.

Hence, in pursuit of C6 and C12 functionalization of TB, we adapted and varied our previously developed conditions,[14] using DMF as the electrophile quench. With TMEDA/*s*BuLi (1 equiv), the aldehyde *rac*-**2** was obtained in poor yield (Scheme 1; see the Supporting Information).



Scheme 1. Formylation of TB (*rac*-**1**) and oxidation to mono-amide *rac*-**3**.

However, upon exposure of a $CDCl_3$ solution of *rac*-**2** to air, a change in color was observed, leading to the isolation and characterization (^{1}H NMR and GC-MS) of *rac*-**3**, which was most probably formed by the aerial oxidation of *rac*-**2** to the corresponding acid followed by oxidative decarboxylation.[15] This finding[16] encouraged the study of the direct oxidation of *rac*-**1** in order to devise a method for the preparation of the potentially fascinating twisted bis-amide analogue *rac*-**4**.

Following the screening of a variety of oxidizing agents (Mn, Cr salts, Ru catalysts, hypervalent iodine), the optimized conditions of $KMnO_4$ (3 equiv) and benzyltriethylammonium chloride (BTEAC) in anhydrous CH_2Cl_2 at reflux for 9 h were established and afforded lactam *rac*-**3** in 25% yield (see the Supporting Information) together with 30% of unreacted starting material.[17] In a second lengthy optimization study, conditions of $KMnO_4$/BTEAC (9 equiv) at reflux in CH_2Cl_2 for 4 h led to the bis-lactam *rac*-**4** in 28% yield, as well as 15% and 5% of the quinazoline by-prod-

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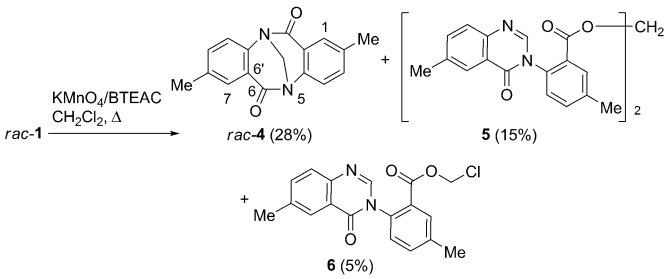


Scheme 2. Synthesis of the twisted bis-amide *rac*-**4** by direct oxidation of TB *rac*-**1**.

ucts **5** and **6** (Scheme 2),[18,19] respectively, whose structures are supported by ^{1}H NMR and HRMS-ESI analysis.

It appears that the use of dichloromethane plays an important role in the reaction since attempts to perform the oxidation reaction in benzene at different temperatures led only to the recovery of the starting material. The structures of *rac*-**4** and **5** were unambiguously established by X-ray diffraction analyses (see Figure 2 and the Supporting Information). Rationalization of the formation of the interesting by-products **5** and **6** relates somewhat to the hydrolytic study in that the N–C(O) bond is cleaved (see below). The incorporation of a methylene in **5** and **6** suggests that a probable mechanism for their formation is first oxidation of the benzylic methylenes to give *rac*-**4** followed by a net oxidative cleavage of the resulting N–C(O) bond that, owing to its twisted nature, is weaker than a normal N–C(O) bond. The carboxylate then undergoes reaction once or twice with dichloromethane in the presence of the phase transfer catalyst to form the corresponding monomeric or dimeric esters, respectively.[20] During these processes, the compound undergoes oxidation to the final dihydroquinazolines **5** and **6**. Dihydroquinazolines are well-known by-products in the synthesis of TB.[21]

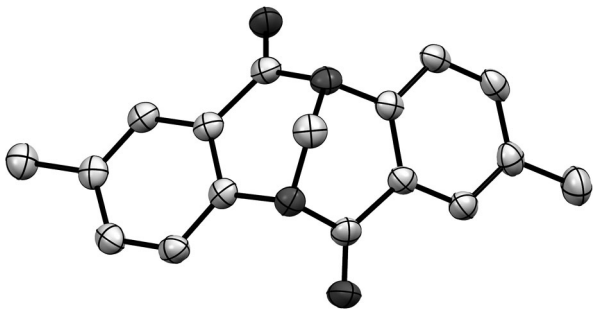
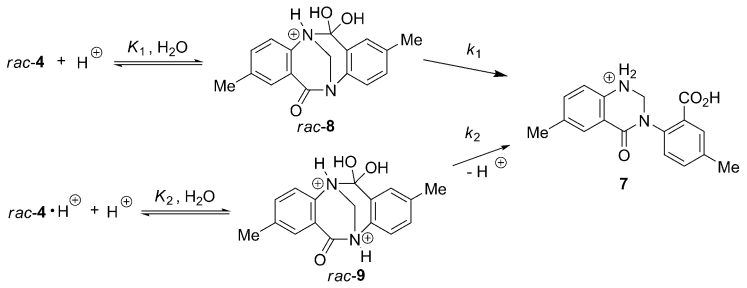


Figure 2. ORTEP representation of the crystal structure of twisted bis-amide *rac*-**4**. Hydrogen atoms, have been omitted for clarity.

X-ray solid-state structure analysis revealed that *rac*-**4** is an example of the relatively rare class of twisted amides (Figure 2).[22] In such amides, steric repulsion or structural constraints impede the overlap of the nitrogen lone-pair electrons with the carbonyl π bond,[23] giving the amide functionality unusual physical and chemical properties. Based on the X-ray structure, the twist angle,[24] describing the deviation from co-planarity between the carbonyl π orbital and the nitrogen lone pair, was determined to be $\tau = -43.7°$ for TB analogue *rac*-**4** as compared to the near $\tau = 0°$ and $\tau = 180°$ commonly found in unconstrained *cisoid* and *transoid* amides, respectively.[24] Furthermore, the overall distortion parameter θ,[25] an additive term that provides a quantitative description of the combined deformation or pyramidality of the nitrogen and carbonyl carbon together with the twist angle, was determined to be $\theta = 106.1°$ (see the Supporting Information), whereas that of a simple planar amide is $\theta = 0°$.[25] Owing to the presence of two such amide functionalities in the molecule, *rac*-**4** is classified as twisted bis-amide, and is, to our knowledge, the first example of such a compound reported to date. Interestingly, twisted bis-amide *rac*-**4** has the shallowest cavity and the longest C2–C8 distance of all TB analogues, including Harding's all-carbon analogue of *rac*-**4**, a diketone of dibenzobicyclo[3.3.1]nonane (see the Supporting Information for comparison).[26] A consequence of the aforementioned deformation is the unusual bond lengths. The crystal structure of *rac*-**4** shows C(O)–N and C=O bond lengths of 1.437 and 1.209 Å, substantially longer and shorter than those of the unconstrained tertiary lactam, 1-methyl-2-piperidone [1.352 and 1.233 Å, respectively ($\tau = 2.5°$ and $\theta = 17.1°$)][27] and similar to the lengths of Kirby's very twisted 1-aza-2-adamantanone [1.475 and 1.195 Å, respectively ($\tau = 90.5°$ and $\theta = 150.0°$)].[23b] (See the Supporting Information for the calculation of θ data.) Abnormal spectroscopic features for the carbonyl group are also common in twisted amides. Twisted bis-amide *rac*-**4** shows an IR absorption at $\tilde{\nu}_{C=O}$ 1694 cm^{-1}. This value is significantly higher than that of unconstrained 1-methyl-2- piperidone ($\tilde{\nu}_{C=O}$ of 1653 cm^{-1})[23c] but not as high as for the twisted 1-aza-2-adamantanone ($\tilde{\nu}_{C=O}$ 1732 cm^{-1}),[23b,c] Interestingly, the IR C=O absorption band of Harding's all-carbon analogue of *rac*-**4**, is at lower frequency ($\tilde{\nu}_{C=O}$ of 1660 cm^{-1}) compared to *rac*-**4**.[28] Based on the comparison of the IR spectra of *rac*-**3** and *rac*-**4**, we suggest that mono- lactam *rac*-**3**, showing $\tilde{\nu}_{C=O}$ 1698 cm^{-1}, is also a twisted amide. The ^{13}C NMR chemical shifts for the carbonyl carbon resonance are also susceptible to variations, although to a much lesser extent.[29] Hence, the shifts of the ^{13}C resonance for *rac*-**4** and 1-methyl-2-piperidone ($\delta = 170.1$ ppm and $\delta = 165$ ppm), do not differ markedly, both being in the range of a regular amide.

To probe the reactivity of the amide functionality of *rac*-**4**, kinetic analyses of its acid-catalyzed hydrolysis was undertaken. The hydrolysis was investigated by ^{1}H NMR spectroscopy in a mixture of CD_3CN/D_2O (8:2). Pseudo-first-order kinetics were observed at different concentrations of DCl (0.058 to 0.87 M) at room temperature. The structurally similar reference compounds, *N*,*N*-dimethylbenzamide and *N*-methylpiperidone, did not undergo hydrolysis in a 0.58 M solution of hydrochloride acid, whereas twisted amide *rac*-**4** was converted to hydrolysis product **7** (Scheme 3) with complete disappearance of *rac*-**4** within 400 min (see the Supporting Information). This difference in reactivity is attributed to the weaker N–C(O) bond in *rac*-**4**. In fact, DFT calcu-



Scheme 3. One kinetic model involving single and double reversible protonation of twisted bis-amide *rac*-**4** followed by reversible formation of two tetrahedral intermediates *rac*-**8** and *rac*-**9**, before irreversible formation of product **7**, in agreement with the experimental data.[32] The structure of *rac*-**8** and *rac*-**9** are suggested and are based on the sites of protonation of *rac*-**4** obtained from the DFT calculations and ^{18}O labeling studies.

lations B3LYP/6-311G**) (see the Supporting Information) show that the preferred site of protonation is on the nitrogen of *rac*-**4**, by 3.5 kcal mol^{-1} compared to oxygen,[30,31] making the N–C(O) bond exceptionally long, 1.61 Å, much longer compared to calculated bond lengths of other *N*-protonated bicyclic lactams.[23f] This facilitates the breaking of the N–C(O) bond in the subsequent nucleophilic addition of water. Interestingly, the DFT calculations show that the LUMO of *N*-protonated *rac*-**4** has almost no contributions from orbitals on nitrogen, but has large lobes on the carbonyl group and the adjacent aromatic carbon, indicating the acylium ion character of *N*-protonated *rac*-**4**. This depiction is further supported by the change in bond angles from 123.5° to 132.5° (C6′–C6–O) and 13.7° to 1.5° (C7–C6′–C6–O) for **4** and *N*-protonated *rac*-**4**, respectively. The latter indicating that the C6–N5 bond is almost broken and that the incipient acylium ion is becoming conjugated with the aromatic moiety of *N*-protonated *rac*-**4**. The hydrolysis rate of *rac*-**4** should be compared to Kirby's twisted amide (see above) for which hydrolysis takes approximately 1 min at very low concentrations of acid,[23b] reflecting its higher twist angle and consequently higher reactivity relative to the amide *rac*-**4**. The product of the hydrolysis, amide **7**, was characterized directly in the reaction mixture by ^1H NMR, 2D NMR, and ESI-MS (see the Supporting Information). As expected, the normal amide **7** does not undergo hydrolysis under the conditions of the reaction. The observed rate constants, k_{obs} were obtained by fitting a single exponential model to the observed decay of starting material at a given concentration of acid, that is, the reaction is first order with respect to *rac*-**4** as the limiting reagent. The quality of the fits was excellent as measured by the regression coefficient, R (see the Supporting Information). The k_{obs} values show a clear dependence on proton concentration and, as seen from Figure 3, the dependence is clearly higher order in $[H^+]$. To explain this behavior, we propose a mechanism involving single and double protonation and nucleophilic attack by water giving intermediates *rac*-**8** and *rac*-**9**, both of which are irreversibly converted to product **7** (Scheme 3). Deriving the rate law from this mechanism gives the expression in Equation (1). Other models were also investigated (see the Supporting Information). Fitting Equation (1) to the experimental data convincingly shows that the denominator is insignificantly different from unity (Figure 3). Thus, Equation (1) simplifies to Equation (2) and, from the fitted values, $k_1K_1 = 6.9 \pm 3.0$ 10^{-3} M^{-1} s^{-1} and $k_2K^1K_2 = 3.2 \pm 0.4$ 10^{-2} M^{-2} s^{-1} were obtained. This implies that at $[H^+] > 0.21$ M, a majority of the product is funneled through the doubly protonated intermediate *rac*-**9**. The fact that the denominator is very close to unity also implies that the equilibria defined by K_1 and K_2 are very strongly shifted towards the left at the investigated concentrations of acid. It has been proposed that hydrolyses of distorted amides occur through the sequential formation of first protonated and then tetrahedral intermediates by equilibrium reactions followed by an irreversible step.[23a] From our data alone it is not possible to distinguish whether waters enters in the reversible or in the irreversible step. To probe for the involvement of reversibly formed tetrahedral intermediates, we performed the hydrolysis of *rac*-**4** using 90% ^{18}O labeled water at 22 °C and $[H^+] = 0.174$ M.

$$k_{obs} = \frac{k_1K_1[H^+] + k_2K_1K_2[H^+]^2}{1 + K_1[H^+] + K_2[H^+]^2} \quad (1)$$

$$k_{obs} = k_1K_1[H^+] + k_2K_1K_2[H^+]^2 \quad (2)$$

A mass analysis of the reaction mixture at approximately 50% conversion (see the Supporting Information) revealed that the distribution of non-^{18}O labeled product **7**, singly ^{18}O labeled **7**, doubly ^{18}O labeled **7**, and triply ^{18}O labeled **7** was approximately 21:100:53:11.[31] The distribution of non-^{18}O labeled to singly ^{18}O labeled starting material *rac*-**4** was approximately 100:7. The ^{18}O-incorporation in *rac*-**4** indicates

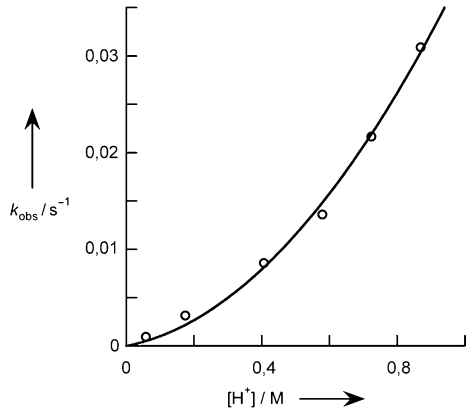


Figure 3. Observed rate constants for the hydrolysis of *rac*-**4** at different concentrations of acid denoted by "o". The fitting of the two kinetic models ([Eq. (1)]; $R = 0.99751$) and ([Eq. (2)]; $R = 0.99754$) to the data denoted by one solid line (both models coincide).

the involvement of reversibly formed, suggested tetrahedral intermediates, *rac*-**8** and *rac*-**9**, that is, water enters in the equilibrium step according to Scheme 3.[33]

In summary, oxidation of the benzylic methylene(s) of TB to carbonyl group(s) has been demonstrated for the first time. The reaction conditions were tuned to produce either the mono- (*rac*-**3**) or the bis- (*rac*-**4**) amide TB analogue. X-ray diffraction analysis revealed *rac*-**4** to be an example of the relatively rare class of twisted amides and, to the best of our knowledge, the first example of a twisted bis-amide. In addition, compound *rac*-**4** has the shallowest cavity of all TB analogues investigated by X-ray diffraction analysis to date. The acidic hydrolysis of *rac*-**4** and "normal" amides was studied and only *rac*-**4** underwent hydrolysis under the concentration of acid employed, yielding amide **7**. Kinetic investigations showed that **7** were formed from singly and doubly protonated intermediates. Labeling studies showed that the decomposition to **7** likely takes place irreversibly from singly and doubly protonated tetrahedral intermediates. The reactivity of twisted bis-amide *rac*-**4** and its analogues is reminiscent of that of β-lactam antibiotics and merits structural–reactivity investigations.[22c]

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Keywords: hydrolysis · oxidation · Tröger's base · twisted amides · X-ray structures

[1] J. Tröger, *J. Prakt. Chem.* **1887**, *36*, 225–245.

[2] a) M. D. Cowart, I. Sucholeiki, R. R. Bukownik, C. S. Wilcox, *J. Am. Chem. Soc.* **1988**, *110*, 6204–6210; b) J. C. Adrian; C. S. Wilcox, *J. Am. Chem. Soc.* **1992**, *114*, 1398–1403, C. S. Wilcox, *J. Am. Chem. Soc.* **1989**, *111*, 8055–8057; c) J. C. Adrian, C. S. Wilcox, *J. Am. Chem. Soc.* **1991**, *113*, 678–680; d) T. H. Webb, H. Suh, C. S. Wilcox, *J. Am. Chem. Soc.* **1991**, *113*, 8554–8555; e) J. C. Adrian; C. S. Wilcox, *J. Am. Chem. Soc.* **1992**, *114*, 1398–1403; f) C. S. Wilcox, J. C. Adrian, T. H. Webb, F. J. Zawacki, *J. Am. Chem. Soc.* **1992**, *114*, 10189–10197.

[3] For the latest reviews, see: a) S. Sergeyev, *Helv. Chim. Acta* **2009**, *92*, 415–444; b) B. Dolenský, J. Elguero, V. Král, C. Pardo, M. Valík, *Adv. Heterocycl. Chem.* **2007**, *93*, 1–56.

[4] a) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497–4498; b) E.-i. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192–11193; c) B. Bhayana, C. S. Wilcox, *Angew. Chem.* **2007**, *119*, 6957–6960; *Angew. Chem. Int. Ed.* **2007**, *46*, 6833–6836; d) F. Hof, D. M. Scofield, W. B. Schweizer, F. Diederich, *Angew. Chem.* **2004**, *116*, 5166–5169; *Angew. Chem. Int. Ed.* **2004**, *43*, 5056–5059; e) F. R. Fischer, W. B. Schweizer, F. Diederich, *Angew. Chem.* **2007**, *119*, 8418–8421; *Angew. Chem. Int. Ed.* **2007**, *46*, 8270–8273.

[5] I. Sucholeiki, V. Lynch, L. Phan, C. S. Wilcox, *J. Org. Chem.* **1988**, *53*, 98–104.

[6] Halogenated TB analogues: a) J. Jensen, K. Wärnmark, *Synthesis* **2001**, 1873–1877; b) A. Hansson, J. Jensen, O. F. Wendt, K. Wärnmark, *Eur. J. Org. Chem.* **2003**, 3179–3188.

[7] Multi-gram scale synthesis of halogenated TB analogues: a) J. Jensen, M. Strozyk, K. Wärnmark, *J. Heterocycl. Chem.* **2003**, *40*, 373–375; b) S. Sergeyev, M. Schär, P. Seiler, O. Lukoyanova, L. Echegoyen, F. Diederich, *Chem. Eur. J.* **2005**, *11*, 2284–2294; c) S. P. Bew, L. Legentil, V. Scholier, S. V. Sharma, *Chem. Commun.* **2007**, 389–391.

[8] Direct halogenation of TB: a) D. Didier, S. Sergeyev, *Eur. J. Org. Chem.* **2007**, 3905–3910; b) M. Faroughi, P. Jensen, A. C. Try, *ARKIVOC* **2009**, *2*, 269–280.

[9] Halogen–lithium exchange: a) J. Jensen, J. Teijler, K. Wärnmark, *J. Org. Chem.* **2002**, *67*, 6008–6014; b) S. Sergeyev, F. Diederich, *Angew. Chem.* **2004**, *116*, 1770–1773; *Angew. Chem. Int. Ed.* **2004**, *43*, 1738–1740; c) Y. Ishida, H. Ito, D. Mori, K. Saigo, *Tetrahedron Lett.* **2005**, *46*, 109–112; d) A. Hansson, T. Wixe, K.-E. Bergquist, K. Wärnmark, *Org. Lett.* **2005**, *7*, 2019–2022; e) J. Artacho, P. Nilsson, K.-E. Bergquist, O. F. Wendt, K. Wärnmark, *Chem. Eur. J.* **2006**, *12*, 2692–2701; f) Z. Jin, S.-X. Guo, X.-P. Gu, L.-L. Qiu, G.-P. Wu, J.-X. Fang, *ARKIVOC* **2009**, *10*, 25–34.

[10] Transition-metal catalyzed cross-couplings: a) ref. 6a; b) J. Jensen, M. Strozyk, K. Wärnmark, *Synthesis* **2002**, 2761–2765; c) U. Kiehne, A. Lützen, *Synthesis* **2004**, 1687–1695; d) C. Solano, D. Svensson, Z. Olomi, J. Jensen, O. F. Wendt, K. Wärnmark, *Eur. J. Org. Chem.* **2005**, 3510–3517; e) F. Hof, M. Schär, D. M. Scofield, F. Fischer, F. Diederich, S. Sergeyev, *Helv. Chim. Acta* **2005**, *88*, 2333; f) D. Didier, S. Sergeyev, *Tetrahedron* **2007**, *63*, 3864–3869; g) U. Kiehne, T. Bruhn, G. Schnakenburg, R. Fröhlich, G. Bringmann, A. Lützen, *Chem. Eur. J.* **2008**, *14*, 4246–4255; h) J. Artacho, K. Wärnmark, *Synthesis* **2009**, 3120–3126.

[11] a) M. Häring, *Helv. Chim. Acta* **1963**, *46*, 2970–2982; b) E. Weber, U. Müller, D. Worsch, F. Vögtle, G. Will, A. Kirfel, *J. Chem. Soc. Chem. Commun.* **1985**, 1578–1580; c) D. A. Lenev, D. G. Golovanov, K. A. Lyssenko, R. G. Kostyanovsky, *Tetrahedron: Asymmetry* **2006**, *17*, 2191–2194; d) C. Michon, M.-E. Gonçalves-Farbos, J. Lacour, *Chirality* **2009**, *21*, 809–817.

[12] a) F. C. Cooper, M. W. Partridge, *J. Chem. Soc.* **1957**, 2888–2893; b) A. Greenberg, N. Molinaro, M. Lang, *J. Org. Chem.* **1984**, *49*, 1127–1130; c) R. A. Johnson, R. R. Gorman, R. J. Wnuk, N. J. Crittenden, J. W. Aiken, *J. Med. Chem.* **1993**, *36*, 3202–3206; d) Y. Hamada, S. Mukai, *Tetrahedron: Asymmetry* **1996**, *7*, 2671–2674.

[13] a) D. A. Lenev, I. I. Chervin, K. A. Lyssenko, R. G. Kostyanovsky, *Tetrahedron Lett.* **2007**, *48*, 3363–3366; b) Q. B. Mahon, D. A. Craig, A. C. Try, *Synthesis* **2009**, 636–642; c) C. Michon, A. Sharma, G. Bernardinelli, E. Francotte, J. Lacour, *Chem. Commun.* **2010**, *46*, 2206–2208; d) A. Sharma, L. Guénée, J.-V. Naubron, J. Lacour, *Angew. Chem. Int. Ed.* **2011**, *50*, 3677–3680.

[14] a) M. Harmata, K. W. Carter, D. E. Jones, M. Kahraman, *Tetrahedron Lett.* **1996**, *37*, 6267–6270; b) M. Harmata, M. Kahraman, *Tetrahedron: Asymmetry* **2000**, *11*, 2875–2879; c) M. Harmata, K.-O. Rayanil, C. L. Barnes, *Supramol. Chem.* **2006**, *18*, 581–586.

[15] For mechanistic inspiration, see: a) H. H. Wasserman, B. H. Lipshutz, A. W. Temper, J. S. Wu, *J. Org. Chem.* **1981**, *46*, 2991–2999; b) C. A.B Rodrigues, M. Norton de Matos, B. M. H. Guerreiro, A. M. L. Gonçalves, C. C. Romão, C. A. M. Afonso, *Tetrahedron Lett.* **2011**, *52*, 2803–2807.

[16] a) One TB being hydroxylated in 6-position has been reported: See reference [14a]; b) for TB-related structures containing oxygen in corresponding 6-position, see: S. G. McGeachin, *Can. J. Chem.* **1966**, *44*, 2323–2328; M. I. Shenbor, G. M. Smirnov, *Vopr. Khim. Khim. Tekhnol.* **1976**, *43*, 24–29 (CA: 87:68019.

[17] The regioselectivity in the benzylic oxidation could be explained by the nitrogen lone-pair stabilization of the benzylic radical or cation formed from the initial hydrogen radical or hydrogen atom abstraction by permanganate. Such stabilization can only take place on carbons 6 and 12 in *rac*-**1**, see: M.-M. Wei, R. Stewart, *J. Am. Chem. Soc.* **1966**, *88*, 1974–1979.

[18] A lesser amount of reagents resulted in lower conversions, while longer reaction times gave lower yields of *rac*-**4** and larger quantities of **5** and **6**.
[19] Interestingly, subjecting the didemethylated TB analogue to the optimized reaction conditions resulted in a decreased yield (9%) of the di-oxygenated product compared to when **1** was used.
[20] K. Holmberg, B. Hansen, *Tetrahedron Lett.* **1975**, *16*, 2303–2306.
[21] a) E. C. Wagner, A. Eisner, *J. Am. Chem. Soc.* **1937**, *59*, 879–883; b) M. Härig, *Helv. Chim. Acta* **1963**, *46*, 2970–2982; c) C. A. M. Abella, M. Benassi, L. S. Santos, M. N. Eberlin, F. Coelho, *J. Org. Chem.* **2007**, *72*, 4048–4054.
[22] a) A. Greenberg, C. M. Breneman, J. F. Liebman in *The Amide Linkage: Selected Structural Aspects in Chemistry, Bio-chemistry, and Materials Science*, Wiley, New York, **2000**; b) for a recent highlight, see: J. Clayden, W. J. Moran, *Angew. Chem.* **2006**, *118*, 7276–7278; *Angew. Chem. Int. Ed.* **2006**, *45*, 7118–7120; c) as an emerging area, see: M. Szostak, J. Aubé, *Org. Biomol. Chem.* **2011**, *9*, 27–35.
[23] a) V. Somayaji, R. S. Brown, *J. Org. Chem.* **1986**, *51*, 2676–2686; b) A. J. Kirby, I. V. Komarov, P. D. Wothers, N. Feeder, *Angew. Chem.* **1998**, *110*, 830–831; *Angew. Chem. Int. Ed.* **1998**, *37*, 785–786; c) A. J. Kirby, I. V. Komarov, N. Feeder, *J. Chem. Soc. Perkin Trans. 2* **2001**, 522–529; d) K. Tani, B. M. Stoltz, *Nature* **2006**, *441*, 731–734; e) M. Szostak, L. Yao, J. Aubé, *J. Am. Chem. Soc.* **2010**, *132*, 2078–2084; f) M. Szostak, L. Yao, J. Aubé, *J. Am. Chem. Soc.* **2010**, *132*, 8836–8837; g) A. Greenberg, D. T. Moore, T. D. DuBois, *J. Am. Chem. Soc.* **1996**, *118*, 8658–8668; h) A. Greenberg, C. A. Venanzi, *J. Am. Chem. Soc.* **1993**, *115*, 6951–6957; i) J. I. Mujika, E. Formoso, J. M. Mercero, X. Lopez, *J. Phys. Chem. B* **2006**, *110*, 15000–15011; j) B. Sliter, J. Morgan, A. Greenberg, *J. Org. Chem.* **2011**, *76*, 2770–2781.
[24] Defined first by F. K. Winkler, J. D. Dunitz, *J. Mol. Biol.* **1971**, *59*, 169–182.
[25] A. J. Kirby, I. V. Komarov, K. Kowski, P. Rademacher, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1313–1316.
[26] A. C. Try, L. Painter, M. M. Harding, *Tetrahedron Lett.* **1998**, *39*, 9809–9812.
[27] F. H. Allen, O. Kennard, D .G. Watson, L. Beammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19.
[28] M. C. Kimber, A. C. Try, L. Painter, M. M. Harding, P. Turner, *J. Org. Chem.* **2000**, *65*, 3042–3046.
[29] S. Yamada, *J. Org. Chem.* **1996**, *61*, 941–946.
[30] Compared with ab initio calculation on analogous protonated 1-azabicyclo[3.3.1]nonan-2-one system, *N*-protonation seems slightly preferred over *O*-protonation (see references [23f,g,i]). However, those calculations were carried out on a lower computational level than ours.
[31] Isodesmic calulations of resonance energies (compare reference [23g]) also support *N*-protonation (see the Supporting Information).
[32] The experimental data cannot distinguish whether *rac*-**8** or *rac*-**4**·H^+ is protonated giving compound **7**.
[33] The ^{18}O incorporation in **7** can be explained by ^{18}O labeled water exchanging with carboxyl group of **7** and attack of ^{18}O labeled water on protonated *rac*-**4**. The amide of **7** is a normal one and thus not reactive. For ^{18}O labeling studies on amides and carboxylic acids, see a) R. S. Brown, A. J. Bennet, H. Slebocka-Tilk, *Acc. Chem. Res.* **1992**, *25*, 481–488; b) R. L. Redington, *J. Phys. Chem.* **1976**, *80*, 229–235, and references therein.

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