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Chiral 1,3-Cyclobutane Amino Acids: Syntheses and Extended Conformations

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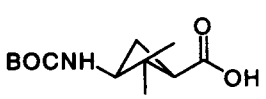
Abstract: Optically active samples of the *N*-protected 1,3-cyclobutane amino acids **1** and **2** were prepared from α-pinene. The synthesis of **1** is enantiodivergent insofar as both optical antipodes of the product can be prepared from the same α-pinene enantiomer. Single crystal X-ray diffraction studies of derivatives of **1** reveal these compounds can have extended conformations.

Protein amino acid surrogates containing small rings can be used to mimic backbone and/or side chain conformations of peptides. Cyclopropane-containing compounds have been used for both these objectives,[1-5] but little or nothing has been published on cyclobutane amino acids[6-8] in this regard. This *Letter* reports syntheses of the cyclobutane amino acids **1** and **2** in optically active form, their transformations into tripeptide mimics, and crystallographic studies revealing essential features of the conformational biases adopted by these amino acids. Amino acid **1** is relatively constrained, having only two important bond rotations. The more flexible compound, **2**, is interesting as a dipeptide surrogate; it has six "chain atoms" similar to two sequential amino acids, but is more rigid since the four membered ring replaces a -$CONHCH_2$- fragment. Both amino acids have potential applications in designed peptidomimetics.



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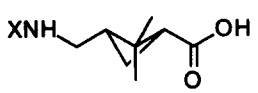
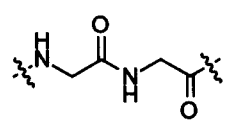
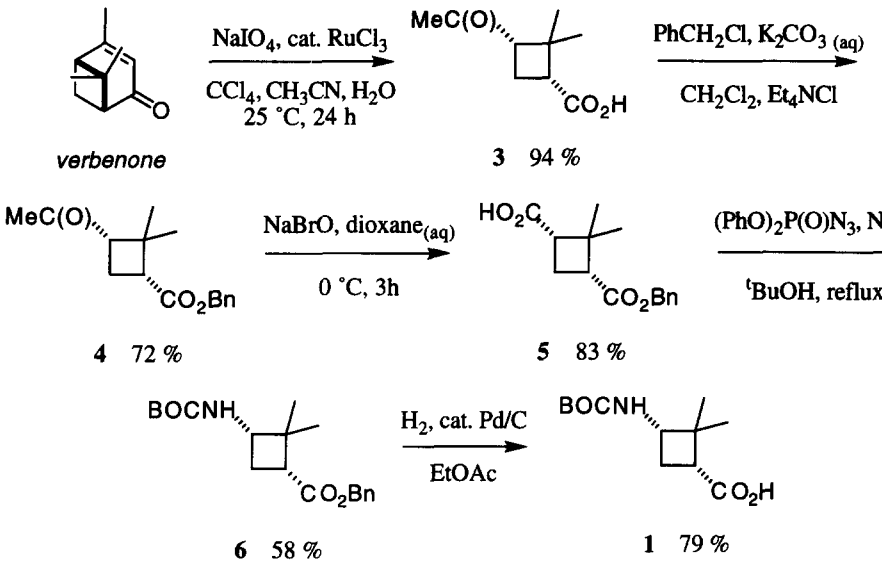


2a X = BOC
2b X = FMOC

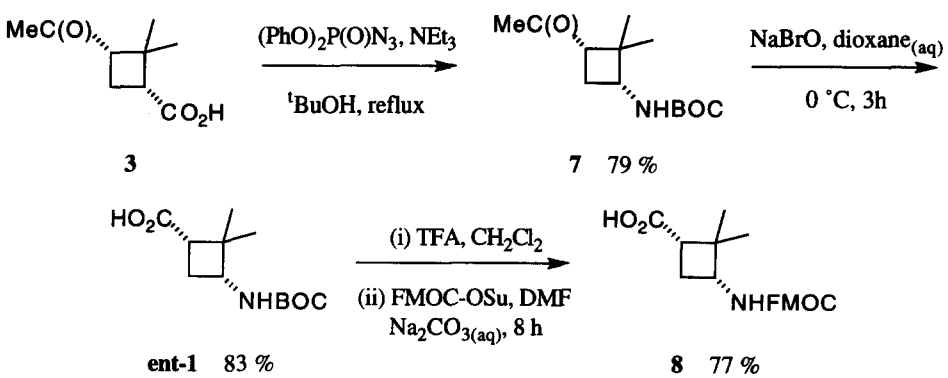


Amino acid **1** was prepared in the following way. Allylic oxidation of (+)-α-pinene via a literature procedure[9] gave verbenone, the starting material for this synthesis. Oxidative cleavage[10] of this enone produced the keto-acid **3** with concomitant loss of CO_2. This acid was benzylated, then subjected to a haloform reaction. Several sets of reaction conditions were attempted for the haloform process; the best found used sodium hypobromite as shown,[11] while the worst afforded little or no product. Curtius rearrangement of

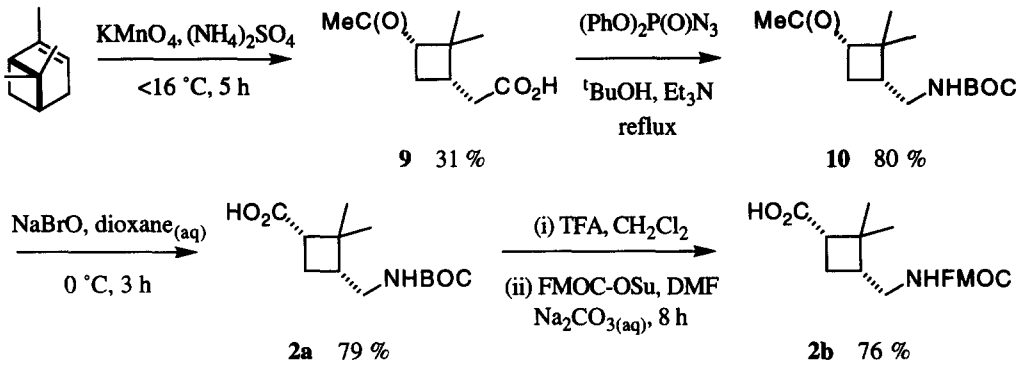
the acid **5** in *tert*-butanol afforded the BOC-protected amine **6**, which was subjected to hydrogenolysis to afford the product **1**, a *N*-protected amino acid suitable for peptide syntheses.



An intermediate in the synthesis above can also be converted to the enantiomeric product **1**, hence the route is enantiodivergent. Specifically, juxtaposition of the steps in the synthesis facilitated the production of the enantiomer of **1**, **ent-1**, from intermediate **3**. To do this, a Curtius rearrangement was performed first giving the *N*-protected amino ketone **7**. A haloform reaction using **7** as the substrate then gave **ent-1**. This particular sample was converted to the FMOC protected amino acid **8**, since FMOC protected amino acids are often superior starting materials for solid phase peptide/peptidomimetic syntheses.[12]



Amino acid **2** was prepared via a sequence very similar to that used to access compound **1**, but directly from (+)-α-pinene and without allylic oxidation to verbenone. Thus direct oxidation of (+)-α-pinene gave the ketoacid **9**.[13] This was then transformed into the product *N*-protected amino acids via sequential Curtius and haloform reactions.



Two model compounds have been prepared to begin to elucidate the conformational biases imposed by incorporating the amino acid surrogates **1** and **2** into peptide sequences. Compound **11** was made by activating **ent-1** with cyanuric fluoride,[14] then coupling with *iso*-propylamine. The tripeptide mimic **12** was prepared from **ent-1** by a solid phase coupling on Kaiser's oxime resin,[15] then cleavage with 2-aminopropane. Single crystals of both these materials were analyzed by X-ray diffraction. Both molecules have an extended conformation; in **11** and **12** intersections of the normals of the planes of the CONH groups are 17.5° and 28°.

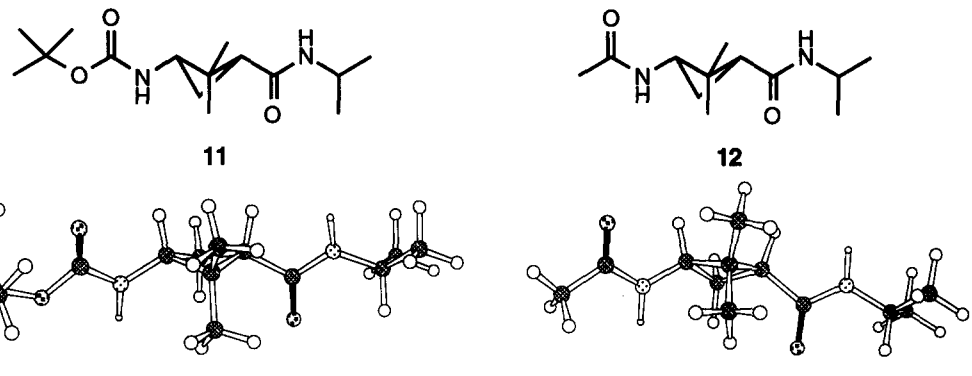


Figure 1. Representations of compounds **11** and **12** generated directly from crystallographic coordinates.

The crystal packing diagram of compound **11** was notable insofar as the molecules stacked with intermolecular hydrogen bonds between the carbamate CO and the amide NH atoms (Figure 2). In this respect the compound has a resemblance to an artificial β-sheet. Conversely, compound **12** did not stack in such a regular arrangement, perhaps implying that sheet conformations are not necessarily common to all compounds in this series. Further studies are in progress to test whether or not derivatives of **1** in conjunction with β-turn mimics can be used to enforce hairpin conformations. In any event, we are optimistic that these amino acids will be useful in syntheses of designed peptidomimetics and combinatorial libraries. They can be prepared in gram amounts and in optically active form.[16] Moreover, the molecular parameters collected in the crystallographic studies described above will provide a basis for parameter sets for molecular modeling of peptidomimetics containing **1** in solution.

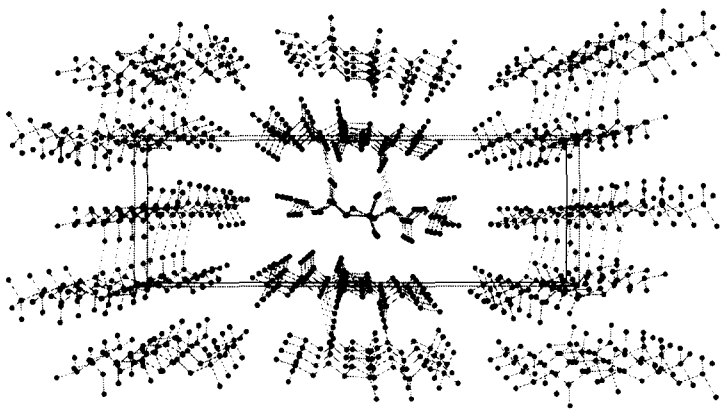


Figure 2. Crystal packing diagram for compound **11** illustrating sheet-like orientations of intermolecularly hydrogen-bonded molecules.

Acknowledgments

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References and Notes

1. Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710.
2. Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron* **1993**, *49*, 3521.
3. Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231.
4. Burgess, K.; Li, W.; Lim, D.; Moye-Sherman, D. *J. Am. Chem. Soc.* **1996**, submitted.
5. Burgess, K.; Ke, C.-Y. *Int. J. Peptide Protein Res.* **1996**, submitted.
6. Avotins, F. *Russian Chemical Reviews* **1993**, *62*, 897.
7. Avotins, F.; Bizdena, E. *Khim. Teknol. Biol. Aktiv. Soedin.* **1983**, 102.
8. Avotins, F.; Gilis, A.; Gudriniece, E.; Spince, B. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1984**, *3*, 339.
9. Lajunen, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **1994**, *35*, 4461.
10. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
11. Auburn, P. R.; MacKenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.
12. Atherton, E.; Sheppard, R. C.*Solid Phase Peptide Synthesis, A Practical Approach*; IRL Press: Oxford. 1989.
13. Wolk, J. L.; Goldschmidt, Z. *Synthesis* **1986**, 347.
14. Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651.
15. DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295.
16. **1:** mp: 161-162 °C; TLC: R_f = 0.35 (33% EtOAc/hexanes); $[\alpha]^{25}_D$: -30.1 (*c* = 1.2, acetone); ^{1}H NMR (200 MHz): δ 10.8 (br, 1H), 4.7 (br, 1H), 3.6-3.9 (m, 1H), 2.50-2.62 (m, 1H), 1.92-2.38 (m, 2H), 1.42 (s, 9H), 1.26 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (50.3 MHz): δ 178.4, 157.8, 80.8, 51.8, 46.4, 41.4, 28.8, 28.3, 23.2, 18.5; IR (KBr): ν (cm^{-1}) 1717.1, 1652.2, 1380.2; MS(FAB): 244 (MH^+); Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70;, N, 5.76; Found: C, 59.14; H, 8.93; N, 5.57. **2a:** mp: 76-77 °C; TLC: R_f = 0.35 (33% EtOAc/hexanes); $[\alpha]^{25}_D$: +8.6 (*c* = 1.2, acetone); ^{1}H NMR (200 MHz): δ 11.4 (br, 1H), 4.5 (br, 1H), 3.08 (m, 2H), 2.71 (t, J = 8.7 Hz, 1H), 2.08 (br, 2H), 1.9 (m, 1H), 1.42 (s, 9H), 1.23 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (50.3 MHz): δ 178.1, 156.0, 79.8, 45.6, 42.2, 41.6, 30.4, 28.4, 22.4, 17.6; IR (KBr): ν (cm^{-1}) 1702.8, 1681.9; MS(FAB): 258 (MH^+). **2b:** mp: 51-53 °C; TLC: R_f = 0.40 (50% EtOAc/hexanes); $[\alpha]^{25}_D$: -14.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz): δ 9.49 (br, 1H), 9.8 (d, J = 3 Hz, 2H), 9.5 (d, J = 3 Hz, 2H), 7.32 (m, 4H), 4.75 (br, 1H), 4.39-4.55 (br, 2H), 4.28 (m, 1H), 2.95-3.31 (br, 2H), 2.64-2.78 (m, 1H), 1.82-2.22 (br, 3H), 1.22 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (50.3 MHz): δ 177.9, 156.3, 143.9, 141.3, 127.7, 127.0, 124.9, 124.8, 119.9, 66.5, 47.3, 45.5, 42.2, 41.5, 30.5, 22.4, 17.5; IR (KBr): ν (cm^{-1}) 1703.8, 1539.1; HRMS(FAB): Calcd for $C_{23}H_{26}O_4$ (MH^+) 380.1862, found 380.1890.

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