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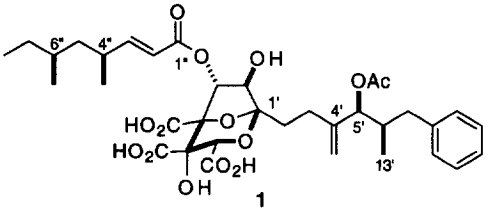
An Enantioselective Solution Towards Synthesizing "Skip" 1,3 Dimethyl Stereocenters. A Synthesis of 4S(2E,4R*,6R*)-4,6-Dimethyl-2-octenoic Acid.

Richard H. Schlessinger* and Kevin W. Gillman

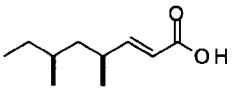
Department of Chemistry, University of Rochester, Rochester, New York 14627

Abstract: A versatile method of synthesizing "skip" 1,3 dimethyl stereocenters via an enantioselective aldol reaction followed by stereoselective catalytic hydrogenation produces three syn contiguous chiral centers. Barton deoxygenation of the intermediary hydroxyl group provides the desired skip 1,3 dimethyl array.

Stereoselective syntheses of remote stereocenters have been the subject of considerable study for synthetic chemists, since this ensemble emerges frequently in a wide variety of biologically interesting natural products. To date, there have been only a handful of successful approaches dealing with acyclic "skip" 1,3 dimethyl stereocenters.[1] In this context, we have completed a novel synthesis of the α,β-unsaturated octenoic acid, **2**, a side chain of zaragozic acid A (**1**), and a substance presenting just such a stereochemical problem.

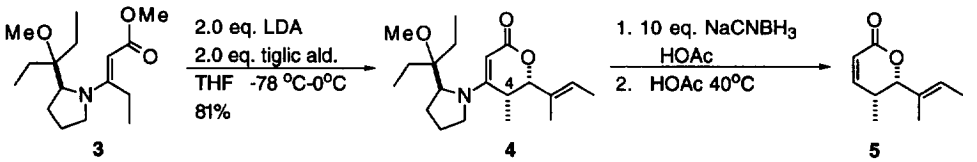


1



2

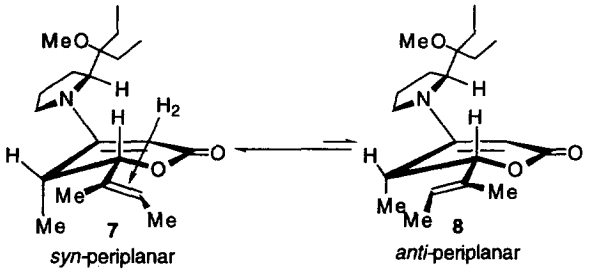
The lithium enolate of vinylogous urethane **3** in THF solution reacts with tiglic aldehyde to afford the vinylogous urethane lactone **4**.[2] **4** was reduced with $NaCNBH_3$ to obtain the unsaturated lactone **5**. Comparison of **5**, obtained in this manner, to a racemic sample of **5** prepared from the diisopropylamine analogue of **3**, show that **4** formed, in the condensation of **3** and tiglic aldehyde, in 81% yield with 97.2% *ee* and 99% *de*.[3]



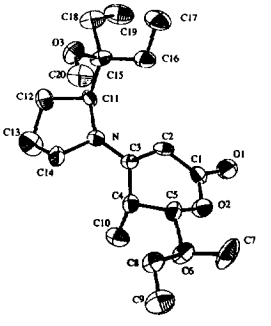
3 **4** **5**

Six membered *syn*-substituted vinylogous urethane lactones like **4** are conformationally rigid, with the C4 methyl group lying axial to the six-membered ring, as determined by single crystal X-ray analysis.[4] Exploiting this rigid backbone to introduce additional stereocenters in the side chain has been a goal of ours for some time. In this instance, it was our desire to reduce the side chain of **4** to obtain the all *syn*-substituted

lactone **6**. MM2 calculations on **4** suggested that the ground state rotational equilibrium of the trisubstituted olefin favored the *syn*-periplanar conformation of the double bond with respect to the lactone oxygen, structure **7**, over the *anti*-periplanar conformation, **8**, by 0.97 Kcal/mol.[5] Hence, we felt that an energetically biased approach of **7** onto the catalyst surface from the face opposite the pseudo-axial methyl group would yield good stereoselectivity in the reduction of **4** to **6**.



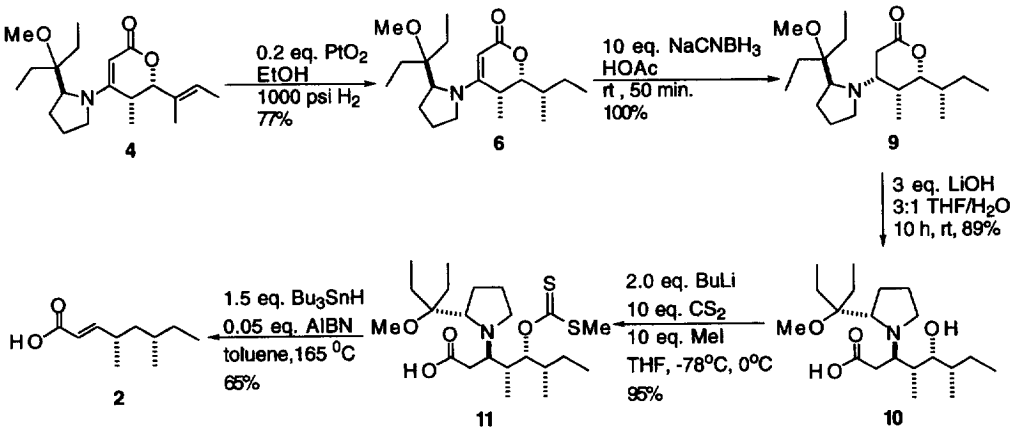
This proved to be the case since reduction of **4** using 20 mol% platinum (IV) oxide[6] in ethanol under 1000 psi H_2 at -20 °C afforded the *syn, syn*-substituted vinylogous urethane lactone **6** as a >10:1 mixture of epimers in 77% yield. The absolute configuration of the major diastereomer as determined by single crystal X-ray analysis is shown below.[7]



6

With the final stereocenter set, synthesis of the α,β-unsaturated acid **2** followed in brief order. Reduction of **6** using sodium cyanoborohydride in glacial acetic acid followed by quenching into 2N sodium hydroxide, and extraction with diethyl ether, gave the β-amino lactone **9** in quantitative yield.[8] Crude **9** was converted into its corresponding β–amino acid **10** by treatment of the former with 3 eq. lithium hydroxide in a 3:1 THF:H_2O solution for 10 h followed by removal of the solvent under vacuum to afford **10** as a white solid.[9] The secondary hydroxyl group of **10** was converted into its corresponding xanthate under conditions somewhat modified from those commonly used.[10] Deprotonation of **10** using 2 eq. of *n*-BuLi in dry THF (-78 °C to 0 °C, 2 h), afforded the corresponding lithium dianion. Addition of 10 eq. carbon disulfide to the dianion at -78 °C followed by warming to room temperature for 3 h formed the intermediate thiocarbonolate

lithium salt. Finally, addition of 10 eq. of methyl iodide, at 0 °C for 5 h, produced the desired xanthate, **11**, as a light yellow powder, 95% yield, after chromatography on silica gel.



11 was then converted into **2** in the following fashion. In a bomb, xanthate **11** was treated with 1.5 eq. Bu_3SnH and 0.05 eq AIBN in 0.05 M dry, deoxygenated toluene. The solution was further degassed with argon, sealed, and heated for 1.5 days at 165 °C.[11] Extraction of the organic layer with 2N sodium hydroxide and re-acidification of the aqueous layer, followed by extraction with diethyl ether produced the α,β-unsaturated acid **2**, virtually free of impurities, in 65% yield.[12] Near quantitative recovery of the chiral auxiliary was easily achieved by extraction of the reaction mixture with 10% HCl followed by adjusting the aqueous layer to pH 14 and extraction with diethyl ether. The synthetic **2** was determined to be identical (^1H NMR, ^{13}C NMR, IR, Chiral HPLC) to the natural acid obtained by chemical degradation of zaragozic acid A.[13]

We feel that this type of synthetic scheme can be used as a general approach towards the synthesis of a wide variety of analogues that possess this interesting stereochemical array. We are currently working on a synthetic sequence directed towards assembling *anti*-dimethyl stereocenters as well as assembling synthetic intermediates that allow for carbon homologations in both directions around the core "skip" stereochemistry.[14]

Acknowledgment. Financial support from the NIH and Merck, Sharp and Dohme is gratefully acknowledged. We also thank Mr. George Rodriguez for help in obtaining X-ray crystallographic data, and Dr. Derek Von Langen[15] for generously providing us with a natural sample of zaragozic acid A.

References and Notes

1. (a) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4712. (b) Nicolaou, K.C.; Yue, E.W.; Naniwa, Y.; De Riccardis, F.; Nadin, A.; Leresche, J.E.; La Greca, S.L.; Yang, Z. *Angew. Chem.Int. Ed. Engl.* **1994**, *33*, 2184. (c) Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.*, **1985**, 1419.

2. For extensive methodological studies on vinylogous urethane lactones possessing a non C_2 symmetric chiral auxilary see: Li Y.J. Ph. D. Thesis 1994, University of Rochester, Rochester N.Y.
3. Racemic **5** was prepared starting from the diisopropylamine analogue of **3** by a route identical to that described for nonracemic **5**. Racemic **5** was chromatographed on a nonracemic HPLC column under conditions which allowed for baseline separation of racemic **5** into its racemates.

Chiral stationary-phase HPLC analyses were performed with a Varian 3010 pump and LDC spectromonitor using a Diacel CHIRALPAK® AD column supplied by Chiral Technologies Inc.. The spectra were recorded with a LDC UV/vis recording spectrometer. UV-vis (EtOH) λs 213 nm; $HPLC_{ret}$ 12.93 (50% **5**), 15.10 (50% ent. **5**), 90:10 hexane:ethanol, 0.5 mL/min. Under identical conditions, nonracemic **5** displayed peaks at 12.94 (98.87% **5**), 15.02 (1.22% ent. **5**).
4. See reference 2.
5. Allinger, N.L. *J. Amer. Chem. Soc.* **1977**, *99*, 8127.
6. Hydrogenations performed using different catalysts, lower H_2 pressures, or warmer reaction temperatures, eroded the stereoselectivity of this transformation.
7. Crystal data for $C_{20}H_{35}NO_3$: orthorhombic, $P2_12_12_1$ (No.19), a = 7.29(3) Å,b = 12.57(1) Å, c = 23.93(7) Å, V = 2194(8) $Å^3$, Z = 4. A total of 4390 reflections (h,,k,$\pm l$)were collected in the range 4° < 2q < 50° with 3805 having I >3.00(I)s being used in the structural refinement by full-matrix least-squares techniques (237 variables) using the TEXSAN crystallographic package from Molecular Structures Corporation. Final R = 0.068, R_w = 0.063.
8. Borch, R. F. *Org. Syn.*, **1972**, *52*, 124..
9. Patel, D.V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C.J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.
10. For a review of the formation of xanthates, see Dunn; R., *Carbon Disulphide in Organic Chemistry*; Ellis Horwood: Chichester, 1989, pp.316-367.
11. (a) Hart, D.J.; Kanai, K. *J. Org. Chem.*, **1982**, *47*, 1555, Barton D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans*, **1975**, 1, 1.
12. Radical induced decarboxylation, most likely of **2**, into its hydrocarbon analogue is to be the only by-product of this reaction. The volatility of this product precluded its isolation and definitive identification.

Racemic **2** was prepared starting with the diisopropylamine analogue of **3** and carrying each intermediate through the appropriate steps. Conversion of the natural, synthetic chiral, and synthetic racemic acids into their corresponding methyl esters with diazomethane afforded suitable chromatographic samples. Racemic **2** was chromatographed on a nonracemic HPLC column under conditions which allowed for baseline separation of racemic **2** into its racemates. Chiral stationary-phase HPLC analyses were performed with a Varian 3010 pump and LDC spectromonitor using a Diacel CHIRALPAK® AD column supplied by Chiral Technologies Inc. The spectra were recorded with a LDC UV/vis recording spectrometer. UV-vis (EtOH) λs 218 nm; column temperature 38.0 °C; $HPLC_{ret}$ 35.89 (50% **2**), 39.09 (50% ent. **2**), 100% hexane, 0.2 mL/min. Under identical conditions, nonracemic **2** displayed a peak at 38.98 identical to the methyl ester derived from natural **2**.
13. Sidebottom, P.J.; Highcock R.M.; Lane, S.J.; Procopiou, P.A.; Watson, N.S. *J.Antibiotics*. **1992**, *45*, 648.
14. Private communication from K. W. Gillman.
15. Merck, Sharp and Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065.

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