A Stereoselective Synthesis of MeBmt Employing a New Chiral Glycine Enolate Derivative

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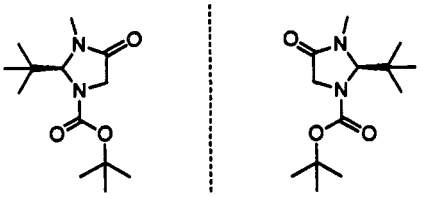
Our contribution to a rapidly growing field of enantioselective synthetic methods for nonproteinogenic amino acids was the development of chiral glycine enolate precursors based on imidazolidinones.[1] Their synthesis was first envisioned starting from serine, but is now more conveniently achieved from glycine itself, in a process involving an enantiomer separation. These chiral glycine building blocks do not depend upon an auxiliary, which would have to be recovered, and offer a convergent entry to higher amino acids. Although the glycine-derived imidazolidinone (*S*)-(−)- or (*R*)-(+)-Boc-BMI (1; Chart I) is the most versatile of the chiral five-membered heterocycles used for the preparation of a variety of amino acids,[1-3] the rather drastic reaction conditions required for the final hydrolysis of the intermediate *N*-methyl amide have limited its utilization to the preparation of amino acids that do not contain acid-sensitive substituents. This problem prompted us to consider oxazolidinones **2** (Chart I) as alternative chiral glycine building blocks.[4] The final deprotection in the case of **2a** is easily accomplished by hydrogenolysis of the benzyloxycarbonyl-(Cbz)-protective group followed by aqueous treatment resulting in the formation of salt-free amino acids. (*R*)- and (*S*)-oxazolidinones **2** are available via resolution by preparative HPLC.[6]

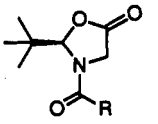
In this paper, we report coupling reactions of **2a** with aldehydes,[7] as exemplified in a total synthesis of MeBmt (**9**),[8] the unusual C-9 amino acid found in the immunosuppressive undecapeptide cyclosporine.[9,10]

Chart I



(*S*)-(−)-**1** (*R*)-(+)-**1**

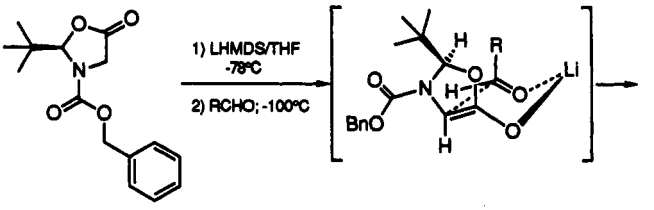
Boc-BMI



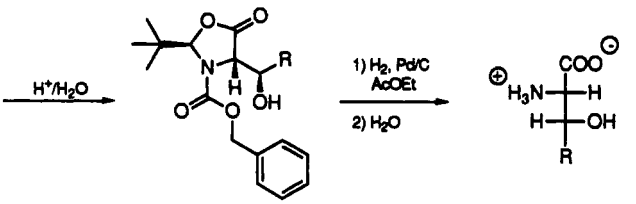
2a R = $C_6H_5CH_2O$-

2b R = C_6H_5-

Scheme I



2a



Problems associated with the instability of the lithium enolate Li-**2a** were overcome by the use of a bulky base lithium hexamethyldisilazide (LHMDS) and by performing the addition reactions at low temperature (−100 °C). Model studies using aromatic aldehydes revealed the stereochemical outcome of the addition reactions (Scheme

(1) Fitzi, R.; Seebach, D. *Angew. Chem.* **1986**, *98*, 363. Erratum: Ibid. **1986**, *98*, 842. Fitzi, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 345. Erratum: Ibid. **1986**, *25*, 766. Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277 (Tetrahedron Symposia-in-Print Number 33, α-Amino Acid Synthesis).

(2) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215.

(3) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237.

(4) (a) Müller, S. G. *Ph.D. Thesis*, No. 8616, ETH Zürich, 1988. (b) Seebach, D.; Müller, S. G.; Gysel, U.; Zimmermann, J. *Helv. Chim. Acta* **1988**, *71*, 1303. See also the references given in ref 5 for previous work with oxazolidinones.

(5) (a) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337. (c) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (d) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, *28*, 2243. (e) Nebel, K.; Mutter, M. *Tetrahedron* **1988**, *44*, 4793.

(6) Preparative HPLC was performed on silica gel coated with the polymer from *N*-acryloylphenylalanine ethyl ester (Chiraspher). Use of a Prepbar chromatography system allowed injections of several grams at a time. (a) Chiraspher and Prepbar are registered trademarks of the E. Merck Company in Darmstadt (Germany). (b) Kinkel, J. N. *GIT-Suppl. 3, Chromatographie* **1988**, *32*, 29. (c) Kinkel, J. N.; Reichert, K.; Knöll, P. *GIT-Suppl. 3, Chromatographie* **1989**, *33*, 104. We thank Dr. J. N. Kinkel, E. Merck (Darmstadt, Germany), for the resolution of a large amount of *rac*-**2a**.

(7) For a review on the stereoselective synthesis of α-amino-β-hydroxy acids, see for example: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; 1st ed.; Pergamon Press: Oxford, 1989. (b) *α-Amino Acid Synthesis*, Tetrahedron Symposia-in-Print Number 33, *Tetrahedron* **1988**, *44*, 5253–5614.

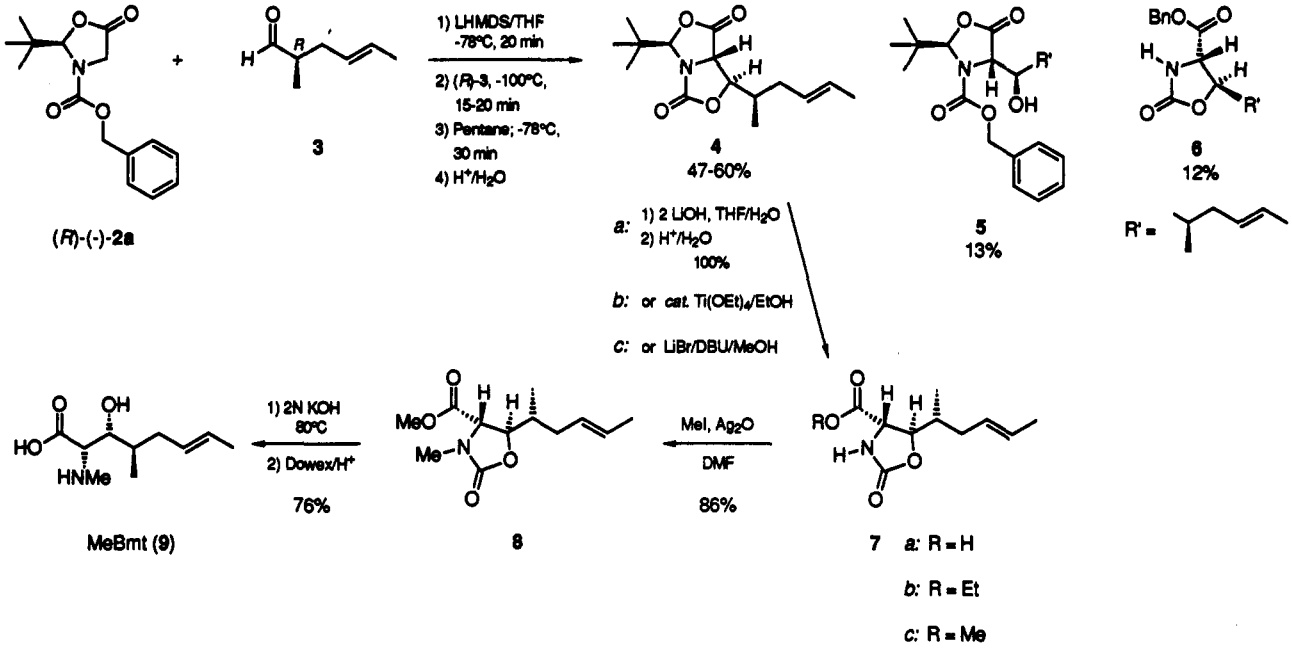
(8) (4*R*)-4-[(*E*)-2-Butenyl]-4,*N*-dimethyl-L-threonine = MeBmt (IUPAC/IUB three-letter amino acid notation).

(9) MeBmt found in cyclosporine appears to be critically involved in the observed biological activity of this chemotherapeutic agent: (a) Cyclosporine A; White, D. J. G., Ed.; Elsevier Biomedical: Amsterdam, 1982. (b) Wenger, R. M. *Angew. Chem.* **1985**, *97*, 88. Wenger, R. M. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 77. (c) Fliri, H. G.; Wenger, R. M. Cyclosporine: Synthetic Studies, Structure–Activity Relationships, Biosynthesis and Mode of Action. In *Biochemistry of Peptide antibiotics. Recent Advances in the Biotechnology of β-Lactams and Microbial Bioactive Peptides*; Kleinkauf, H., von Döhren, H., Eds.; Walter de Gruyter: New York, 1990.

(10) Of the eleven synthetic approaches to MeBmt reported to date, three are based on the aldol methodology using a chiral glycine building block: (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (b) Togni, A.; Pastor, S. D.; Rihs, G. *Helv. Chim. Acta* **1990**, *72*, 1471. (c) See ref 3. Using an achiral glycine derivative: (d) Schmidt, U.; Siegel, W. *Tetrahedron Lett.* **1987**, *28*, 2849. (e) Aebi, J. D.; Dhaon, M. K.; Rich, D. H. *J. Org. Chem.* **1987**, *52*, 2881. First total synthesis of MeBmt: (f) Wenger, R. M. *Helv. Chim. Acta* **1983**, *66*, 2308. Total syntheses of MeBmt involving the Sharpless asymmetric epoxidation: (g) Tung, R. D.; Rich, D. H. *Tetrahedron Lett.* **1987**, *28*, 1139. (h) Sun, C. Q.; Rich, D. H. *Tetrahedron Lett.* **1988**, *29*, 5205. (i) Rama Rao, A. V.; Murali Dhar, T. G.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron Lett.* **1988**, *29*, 2069. (j) Rama Rao, A. V.; Murali Dhar, T. G.; Subhas Bose, D.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron* **1989**, *45*, 7361. Total synthesis of MeBmt from D-glucofuranose: (k) Rama Rao, A. V.; Yadav, J. S.; Chandrasekhar, S.; Srinivas Rao, C. *Tetrahedron Lett.* **1989**, *30*, 6769. Total synthesis of MeBmt from D-serine: (l) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511.

0022-3263/91/1956-6230$02.50/0

Scheme II[18]



I):[11,12] as expected from previous work,[2,3,5] the oxazolidinone enolate Li-**2a** reacts with aldehydes exclusively from the side opposite to the bulky *t*-Bu group (*ul*-1,3-induction[13]) and the coupling of the two trigonal centers occurs selectively with relative topicity *lk*.[13]

Having established the stereochemical course of the aldol addition reaction, we proceeded to a total synthesis of MeBmt. The side chain of MeBmt requires (2*R*,4*E*)-2-methyl-4-hexenal (**3**) (Scheme II) as the electrophile. This aldehyde was prepared from the corresponding alcohol[14] by Swern oxidation following the literature procedure.[15] While the starting alcohol was of 92% ee, the product aldehyde was found to be of only 76% ee.[16] The tendency of this aldehyde to racemize has been noted earlier.[10a] While it was certainly not an ideal situation, we decided to carry on with this enantioenriched (er) substrate since the chiral glycine enolate (*R*)-Li-**2a** was enantiopure (ep) and the resulting diastereomeric products could be separated at a later stage.[17] Thus, the aldol addition reaction was performed under the optimized reaction conditions (LHMDS, −100 °C, 20 min). The expected aldol adducts (epimeric mixture)[18] were obtained only as minor products. The major product was, to our surprise, the bicyclic carbamate **4** (Scheme II), which had not been observed in the series with aromatic aldehydes.[19] The unexpected product **4**, which was first regarded as a troublesome and unwanted byproduct, turned out to be "just right" in view of our goal, the synthesis of MeBmt. In a subsequent study with aldol product **5**, a major problem had been a retro-aldol reaction. With the bicyclic carbamate **4**, the serendipitous protection of the hydroxy group avoids the danger of retro-aldol reaction. Furthermore, as the Cbz group is removed (yet the nitrogen is still protected), we are relieved of potential complications of the originally planned hydrogenolysis step due to the presence of a C–C double bond in the side chain.[20]

Therefore, we first concentrated our efforts in maximizing the production of the bicyclic oxazolidinone **4**.[21a] The highest conversion was obtained when the aldolate reaction mixture was transferred to twice its volume of pentane, precooled at −78 °C. After the mixture was stirred for 30 min at this temperature, aqueous workup was followed by chromatographic purification to yield the desired **4** in 47–60% yield, along with the aldol product **5** (13%) and the benzyl ester **6** (12%).[21]

With the stable compound **4** in hand, the route to MeBmt was now straightforward. Three different sets of reaction conditions enabled us to achieve the selective cleavage of the acetal ring: the Ti(IV)-catalyzed transesterification method,[22] the LiBr/DBU transesterification procedure,[23] or the saponification with LiOH. We chose

(11) Details of the stereochemical analysis will be reported elsewhere: Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, in press.

(12) Addition reactions with aliphatic aldehydes are believed to proceed in the same stereochemical manner as evidenced in at least one chemical correlation with a known compound. See ref 11.

(13) Seebach, D.; Prelog, V. *Angew. Chem.* **1982**, *94*, 696. Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

(14) The sample was kindly provided to us by Sandoz Pharma AG (Basel, Switzerland).

(15) The chiral aldehyde (2*R*,4*E*)-2-methyl-4-hexenal (**3**) can be prepared according to published procedures: (a) See ref 10a. (b) Deyo, D. T.; Aebi, J. D.; Rich, D. H. *Synthesis* **1988**, 608.

(16) The enantiomeric excess was measured by capillary GC on a peracylated cyclodextrine chiral stationary phase (Octakis(3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin in OV 1701 Vi (1:2): König, W. A.; Krebber, R.; Mischnick, P. *J. High Resolut. Chromatogr.* **1989**, *12*, 732).

(17) In earlier experiments with *rac*- or partially enantioenriched **3** and *rac*- or enantiopure (*R*)-**2a**, we observed no kinetic resolution. Cf. ref 3. This also means that our chiral heterocyclic enolates react with α-branched chiral aldehydes under socalled "reagent control".

(18) The enantiomeric purity (76% ee) of aldehyde **3** was reflected in the isolation of an ~7.5:1 epimeric mixture for each of the crude products **4**–**9** (Scheme II) (ratio determined by 200-MHz ^{1}H NMR).

(19) The tendency for cyclization observed with the aldol products from α-substituted aliphatic aldehydes reminds us of the Thorpe–Ingold effect: Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. For a recent review article, see: Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(20) A diastereomeric erythro aldol product, if ever formed via *ul* coupling of the two trigonal centers (cf. Scheme II), would not cyclize to a bicyclic carbamate of type **4** due to steric hindrance. Easy separation of **4** from uncyclized **5** (or its diastereoisomer) spares us purification of diastereoisomers and constitutes another practical advantage.

(21) (a) Most of the optimization was carried out with isobutyraldehyde as a model electrophile. (b) Various Lewis acids or bases, either in situ immediately following the coupling reaction or on the crude aldol product, proved to be ineffective in forcing the bicyclization reaction. (c) Recently, we observed that the conversion of the aldol **5** to the desired bicyclic carbamate **4** was realized in 60% yield by treating a THF solution of **5** with 5 mol % of LiSEt at rt for 30 h.

(22) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

the simple hydrolysis with LiOH in THF/H_2O (3:1), since this procedure yielded the carboxylic acid **7a** very rapidly and quantitatively at 0 °C (Scheme II). *N*-Methylation was readily performed following a literature procedure using MeI and Ag_2O in DMF.[24] The product 8 (Scheme II), a known precursor of MeBmt,[10a] was converted to the final amino acid following the procedure of Wenger.[10f] The crude product was first purified by ion-exchange chromatography, and the resulting product, still a 7.5:1 mixture of epimers,[18] was further purified by crystallization to afford in 76% yield the desired MeBmt **9** in diastereo- and enantio pure form.

In conclusion, we have demonstrated the utility of the chiral oxazolidinone **2a** for the synthesis of threonine analogues. With its easy deprotection conditions, this new auxiliary-independent chiral glycine building block will hopefully find much use and become part of the arsenal of synthetic chemists.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from potassium metal/benzophenone ketyl prior to use. Hexamethyldisilizane (HMDS) was distilled from CaH_2 and stored over 4-Å molecular sieves. *n*-BuLi was purchased from the Metallgesellschaft, Frankfurt/Main (Germany), as a 1.56 M solution in hexane. The chiral aldehyde **3** was prepared according to the procedure of Evans.[10a] Anhydrous pentane was stored over 4-Å molecular sieves. All other commercial reagents were used as received. All reactions involving air- or moisture-sensitive compounds were performed under a dry argon atmosphere in oven-dried (120 °C, 12 h) glassware. Flash column chromatography (FC) was performed on Fluka silica gel 60 (230–400 mesh) according to the procedure of Still.[25] Optical rotations were measured at 20 °C (ambient temperature) in $CHCl_3$ unless otherwise stated. IR spectra were recorded as $CHCl_3$ solutions or KBr discs; the values of the absorption bands are expressed in wave numbers ($\tilde{\nu}$) (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts (δ) are reported in ppm downfield of TMS ($\delta = 0$), and coupling constants, *J*, are given in Hz. Fragment ions of MS spectra are indicated in *m/z* units with relative intensities in parentheses. Melting points were uncorrected.

(2*R*,5*S*,6*R*)-1-Aza-2-*tert*-butyl-3,7-dioxa-4,8-dioxo-6-[(1′*R*,3′*E*)-1′-methyl-3′-pentenyl]bicyclo[3.3.0]octane (4). A solution of HMDS (1.37 mL, 6.6 mmol) in 20 mL of THF was cooled to −78 °C followed by dropwise addition of *n*-BuLi (4.2 mL, 6.6 mmol). The resulting solution was stirred at −78 °C for 30 min and transferred via cannula into a solution of (*R*)-**2a** (1.66 g, 6 mmol) in 75 mL of THF, which had been precooled to −78 °C. The resulting pale yellow enolate solution was stirred for an additional 20 min at −78 °C and then cooled to −100 °C (liquid N_2/Et_2O bath). Freshly prepared (2*R*,4*E*)-2-methyl-4-hexenal **3** (1.1 mL, 9 mmol) was then added dropwise, and stirring was continued for 20 min at −100 °C. The aldolate solution was then transferred via cannula as rapidly as possible into 220 mL of cold (−78 °C) pentane. The mixture was stirred for 30 min at −78 °C. Finally, the reaction was quenched by the addition of 12 mL of a 1 N solution of acetic acid in THF and, after stirring for 2 min, immediately poured into 100 mL of aqueous saturated NH_4Cl solution. The organic phase was separated and the aqueous layer extracted with 100 mL of Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated by rotatory evaporation to give the crude product. Purification by FC (hexane/CH_2Cl_2/Et_2O (30:25:3)) gave 793 mg (47%) of the title compound **4** as a white amorphous solid. According to ^1H NMR, this compound was contaminated with ~11.7% of the corresponding C(1′) epimer which could not be removed, neither chromatographically nor by recrystallization (see ref 18): R_f 0.39 (hexane/CH_2Cl_2/Et_2O (30:25:3)); mp 132.8–135.0 °C; $[\alpha]_D$ 60.4 (*c* 1.05);[18] IR (KBr) $\tilde{\nu}$ 3020 w, 2960 m, 2940 m, 2880 w, 1790 s, 1775 s, 1480 w, 1470 w, 1440 w, 1400 w, 1365 m, 1345 m, 1280 w, 1260 w, 1230 s, 1205 m, 1170 m, 1100 w, 1070 w, 1035 m, 1000 m; ^1H NMR (400 MHz) δ 1.02 (d, J = 5.3, 3 H, 1′-CH_3), 1.03 (s, 9 H, *t*-Bu), 1.68 (d, J = 6.3, 3 H, CH_3CH=CH), 1.94–2.04 (m, 2 H, $-CH_2-$), 2.18–2.26 (m, 1 H, 1′-H), 4.01 (d, J = 4.3, 1 H, 5-H), 4.55 (dd, J_1 = 5.9, J_2 = 4.5, 1 H, 6-H), 5.35–5.42 (m, 1 H, =CH–), 5.43 (s, 1 H, 2-H), 5.50–5.60 (m, 1 H, =CH–); minor epimer 1.02 (d, 3 H, 1′-CH_3), 1.03 (s, 9 H, *t*-Bu), 1.68 (d, J = 6.3, 3 H, CH_3CH=CH), 1.94–2.04 (m, 2 H, $-CH_2-$), 2.18–2.26 (m, 1 H, 1′-H), 3.99 (d, J = 4.4, 1 H, 5-H), 4.64 (dd, J_1 = 4.4, J_2 = 4.4, 1 H, 6-H), 5.35–5.42 (m, 1 H, =CH–), 5.43 (s, 1 H, 2-H), 5.50–5.60 (m, 1 H, =CH–); ^{13}C NMR (100 MHz) δ 13.83, 17.95, 24.09, 35.12, 36.75, 37.63, 58.14, 81.85, 100.25, 126.64, 128.72, 161.19, 171.94; minor epimer 13.28, 17.97, 24.10, 34.30, 36.75, 38.03, 58.70, 82.44, 100.30, 127.11, 128.77, 161.27, 171.97; MS *m/z* 281 ($M^{\bullet+}$) (44), 237 (5), 224 (8), 196 (14), 180 (28), 168 (30), 152 (34), 142 (46), 138 (34), 124 (32), 107 (83), 95 (81), 82 (61), 70 (50), 57 (92), 41 (73), 28 (41), 18 (100). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.06; H, 8.24; N, 4.90.

(4*S*,5*R*)-5-[(1′*R*,3′*E*)-1′-Methyl-3′-pentenyl]-2-oxazolidinone-4-carboxylic Acid (7a). A solution of **4** (479 mg, 1.7 mmol) (~7.5:1 C(1′)-epimeric mixture) in 18 mL of THF/H_2O (v/v (3:1)) was cooled in an ice bath and treated with 8.14 mg (3.4 mmol, 2 equiv) of LiOH. After 20 min of stirring at ~0 °C, this colorless solution was acidified to pH 2–3 by carefully adding 2 N HCl solution. The mixture was diluted with 5 mL of water and extracted twice with 20 mL of AcOEt. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to yield 363 mg (quantitative yield) of the title compound as a white powder, which was used in the next step without further purification: $[\alpha]_D$ 74.2 (*c* 1.78);[18] ^1H NMR (200 MHz) δ 0.98 (d, J = 6.1, 3 H, 1′-CH_3), 1.67 (d, J = 5.4, 3 H, CH_3CH=CH), 1.77–2.05 (m, 2 H, $-CH_2-$), 2.10–2.32 (m, 1 H, 1′-H), 4.18 (d, J = 4.7, 1 H, 4-H), 4.55 (dd, J_1 = 5.1, J_2 = 4.7, 1 H, 5-H), 5.25–6.60 (m, 2 H, –CH=CH–), 7.22 (s, 1 H, NH), 9.76 (br s, 1 H, COOH); minor epimer 0.98 (d, J = 6.1, 3 H, 1′-CH_3), 1.67 (d, J = 5.4, 3 H, CH_3CH=CH), 1.77–2.05 (m, 2 H, $-CH_2-$), 2.10–2.32 (m, 1 H, 1′-H), 4.18 (d, J = 4.7, 1 H, 4-H), 4.63 (dd, J_1 = 4.6, J_2 = 4.4, 1 H, 5-H), 5.25–6.60 (m, 2 H, –CH=CH–), 7.22 (s, 1 H, NH), 9.76 (br s, 1 H, COOH); ^{13}C NMR (50 MHz) δ 13.19, 17.42, 33.62, 37.29, 55.94, 82.27, 127.33, 127.92, 160.33, 173.59; minor epimer 12.41, 17.42, 34.73, 37.18, 56.45, 82.76, 126.97, 127.97, 160.42, 173.68.

Methyl (4*S*,5*R*)-3-Methyl-5-[(1′*R*,3′*E*)-1′-methyl-3′-pentenyl]-2-oxazolidinone-4-carboxylate (8). Following the procedure of Olsen,[24] methyl iodide (0.85 mL, 13.6 mmol, 8 equiv) was added to a solution of **7a** (363 mg, 1.7 mmol) in 12 mL of anhydrous DMF. Ag_2O (1.58 g, 6.8 mmol, 4 equiv) was then added, and the resulting dark blue grey suspension was stirred at room temperature for 5 h. This mixture was then filtered through a Celite pad and the solid washed thoroughly with 8 mL of DMF. The filtrate was then diluted with 80 mL of $CHCl_3$. The organic phase, in which a precipitate had formed, was washed twice with 50 mL of a 5% aqueous KCN solution and several times with water, and finally dried over Na_2SO_4. Evaporation of the solvent in vacuo yielded 375 mg of a pale yellow oil. Purification of the crude product by FC (hexane/AcOEt (2:1)) afforded 352 mg (86%) of the title compound as a colorless oil that contained ~11.7% of the corresponding C(1′)-epimer (see ref 18): $[\alpha]_D$ 36.4 (*c* 1.44),[18] $[\alpha]_D$ 38.2 (*c* 1.36, CH_2Cl_2)[18] [lit.[10a] $[\alpha]_D$ 37.1 (*c* 1.51, CH_2Cl_2)]. The spectroscopic data (IR, ^1H and ^{13}C NMR) of the major component were in good agreement with reported ones.[10a] Minor epimer: ^1H NMR (200 MHz) δ 0.91 (d, J = 6.6, 3 H, CH_3CH), 1.63 (d, J = 5.8, 3 H, CH_3CH=CH), 1.83–2.00 (m, 2 H, $-CH_2-$), 2.07–2.25 (m, 1 H, 1′-H), 2.87 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 3.94 (d, J = 5.0, 1 H, 4-H), 4.24 (dd, J_1 = 6.1, J_2 = 4.8, 1 H, 5-H), 5.28–5.60 (m, 2 H, –CH=CH–); ^{13}C NMR (100 MHz) δ 13.86, 17.98, 30.15, 35.22, 37.77, 52.89, 61.77, 78.76, 127.57, 128.15, 157.49, 170.25; MS *m/z* 241 ($M^{\bullet+}$) (60), 182 (96), 156 (39), 138 (81), 128 (95), 109 (43), 100 (76), 84 (63), 67 (31), 55 (88), 42 (100), 29 (52). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.61; H, 8.18; N, 5.69.

(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid (MeBmt) (9). According to the procedure of Wenger,[10f] an aqueous solution of 8 (307 mg, 1.27 mmol) in 6.7

(23) Seebach, D.; Ko, S. Y.; Thaler, A.; Blaser, D. *Helv. Chim. Acta* **1991**, *74*, 1102.
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mL of 2 N KOH was heated at 80 °C with stirring for 3 h. This basic solution was cooled to room temperature and the title compound isolated according to the procedure of Rich.[10e] The basic solution was acidified with Dowex 50 W×8 (H^+ form; 100–200 mesh) to pH <4 and heated again for 5 min at 80 °C. The mixture of Dowex H^+/water was filtered through ca. 30 mL of Dowex 50 W×8 (H^+ form: 100–200 mesh). The desired amino acid was finally eluted with 200–250 mL of an aqueous 1.5 N NH_3 solution. The desired fractions (ninhydrine-active) were combined and evaporated in vacuo to dryness. The colorless residue was then taken up twice in some water and each time concentrated to dryness. The residue[18] was recrystallized from MeOH/H_2O to yield 194 mg (76%) of very fine crystals of MeBmt in diastereomerically and enantiomerically pure form: $[\alpha]_D$ 12.3 (c 0.43, phosphate buffer Titrisol pH 7.00 from Merck) [lit.[10f] $[\alpha]_D$ = 13.5 (c 0.50, phosphate buffer Titrisol pH 7.00 from Merck); lit.[10a] $[\alpha]_D$ 11.4 (c 0.50, phosphate buffer Titrisol pH 7.00 from Merck)]; mp 243–245 °C dec (lit.[10f] mp 240–241 °C; lit.[10a] mp 242–243 °C). The spectroscopic data (IR, ^1H NMR) of this compound were in good agreement with reported ones:[10a,f] ^{13}C NMR (100 MHz, D_2O) δ 18.06, 19.88, 35.26, 36.33, 38.20, 69.33, 76.80, 130.60, 131.43, 174.73. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.57; H, 9.65; N, 6.81.

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Registry No. (*R*)-**2a**, 119323-03-4; **3**, 104372-54-5; **4**, 135646-39-8; **4** (C1′-epimer), 135684-43-4; **5**, 135646-40-1; **6**, 135646-41-2; **7a**, 81135-60-6; **7a** (C1′-epimer), 135684-44-5; **8**, 104324-29-0; **8** (C1′-epimer), 122090-71-5; **9**, 59865-23-5.

A Versatile Transformation of *vic*-Diols into α-Hydroxy Ketones with Hydrogen Peroxide Catalyzed by Peroxotungstophosphates

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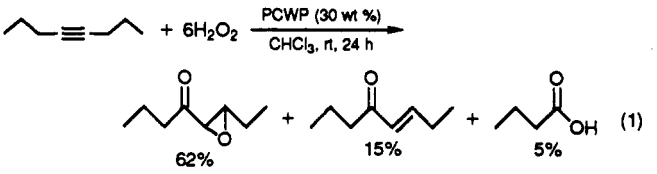
α-Hydroxy ketones (α-ketols), which are versatile starting materials in organic synthesis, are classically synthesized by the acyloin condensation of esters,[1] but this method suffers from a serious limitation in the preparation of cyclic and unsymmetrical aliphatic α-ketols. In order to overcome this limitation, a number of synthetic methods have been developed for the preparation of cyclic α-ketols (e.g., oxidation of silyl enol ethers with *m*-CPBA,[2] treatment of *vic*-diols with Fetizon reagent[3] or Corey–Kim reagent,[4] or permanganate oxidation of olefins[5]) and for aliphatic α-ketols (e.g., mercuric-assisted hydrolysis of α-hydroxy alkyl dithioketals,[6a] hydration of propargylic alcohols,[5b,7] oxidation of ketones with iodosobenzene,[8] DMSO oxidation of oxiranes,[9] treatment of iodocarbonates with fluoride anion on polymeric support,[10] or Ni(II)-catalyzed oxygenation of silyl enol ethers[11]). In general, Swern oxidation of diols results in formation of dicarbonyl compounds.[12]

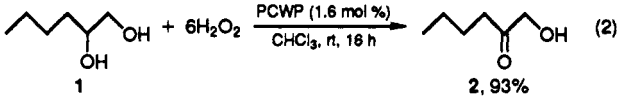
The application of metal reagents such as chromium(IV) or permanganate, which are often used for ketonization of alcohols, to the oxidation of *vic*-diols led to carbon–carbon bond scission to form carboxylic acids.[13] Periodate[14] or lead tetraacetate oxidations[15] of *vic*-diols are well-known methods leading to aldehydes. On the other hand, *vic*-diols have been cleaved to carboxylic acids by hydrogen peroxide under the influence of WO_4^{3-}/PO_4^{3-},[16] $[Me(CH_2)_{15}C_5H_5N]_3PW_{12}O_{40}$ (CWP),[17] or H_2WO_4.[18] However, the oxidative dehydrogenation of *vic*-diols into α-hydroxy ketones has been difficult to achieve in satisfactory yields.

In a preceding paper,[19] we reported that peroxotungstophosphate (PCWP), which can be readily prepared by treating 12-tungstophosphoric acid (WPA) in aqueous hydrogen peroxide with cetylpyridinium chloride (CPC), catalyzed a novel oxidation of internal alkynes into α,β-epoxy ketones and α,β-unsaturated ketones with 35% H_2O_2 in a biphasic system using chloroform as the solvent (eq 1).



(1)

We now report the transformation of *vic*-diols into α-hydroxyketones via a catalytic process employing the PCWP–H_2O_2 system. The reaction was achieved by the use of 35% H_2O_2 (6 equiv) in the presence of PCWP (1.6 mol %) in a biphasic system using chloroform as the solvent (eq 2, Table I).



(2)

Primary–secondary diols were dehydrogenated with high chemoselectivity to form 1-hydroxy-2-alkanones in good

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