Tetrahedron Letters, Vol.31, No.21, pp 3031-3034, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A NOVEL SYNTHESIS OF THE (2*R*,3*S*)- AND (2*S*,3*R*)-3-AMINO-2-HYDROXYCARBOXYLIC ACID DERIVATIVES, THE KEY COMPONENTS OF A RENIN INHIBITOR AND BESTATIN, FROM METHYL (*R*)- AND (*S*)-MANDELATE

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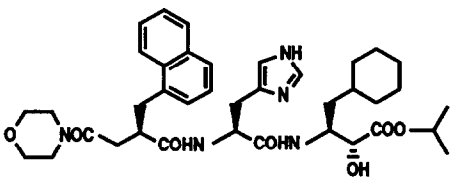
Abstract: The title synthesis could be accomplished by featuring the [2+2]-cycloaddition reaction of a chiral imine with benzyloxyketene, alcoholysis of the formed 2-azetidinone derivative, and reductive removal of the mandelate-derived benzylic oxygen by way of a 2-oxazolidone derivative.

Optically active 3-amino-2-hydroxycarboxylic acid derivatives are often involved in medicinally important compounds as their key components. Thus, one of the promising renin inhibitor (**1**)[2] bears isopropyl (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyrate (**2**)[2,3] as its C-terminal moiety, and bestatin(**3**), the famous immunological response modifier,[4] consists of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid (**4**)[3d,5] and (*S*)-leucine.

We wish to report here a novel synthesis of these antipodal compounds (**2** and **4**) starting from methyl (*R*)-and (*S*)-mandelate (**5** and ent-**5**). The explored synthetic scheme features the [2+2]-cycloaddition reaction of a chiral imine with benzyloxyketene, alcoholysis of the formed 2-azetidinone derivative, and reductive removal of the mandelate-derived benzylic oxygen by way of a 2-oxazolidone derivative. It was previously disclosed that the [2+2]-cycloaddition reaction of chiral imine having an asymmetric center on the nitrogen atom of C=N bond with benzyloxyketene was unrewarding for the preparation of **2** because of its low diastereoselectivity.[3c] However, we have now found that a chiral imine derived from **5** or ent-**5**, which bears an asymmetric center on the carbon atom of C=N bond, can react with benzyloxyketene in a highly diastereoselective manner and the 2-azetidinone derivative produced as a major addition product can be ingeniously elaborated to **2** or **4**.



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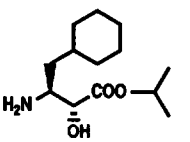

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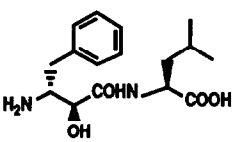

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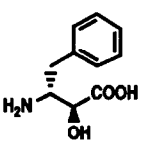

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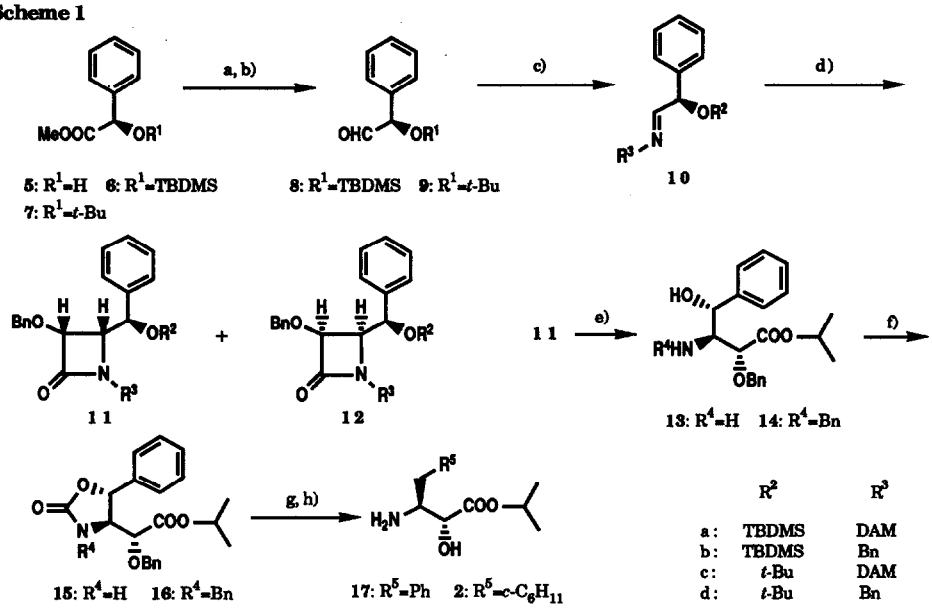
As shown in **Scheme 1**, the synthesis of **2** commences with protection of the hydroxy group of **5** with *t*-butyldimethylsilyl (TBDMS) or *t*-butyl (*t*-Bu) group.[6] These protective groups were employed since they can be readily removed under the conditions for acidic alcoholysis of a 2-azetidinone derivative (*vide infra*). Reduction of the protected esters (**6** and **7**) with diisobutylaluminum hydride (DIBAL) smoothly produced the corresponding aldehydes (**8** and **9**).[6] Two sorts of the aldehydes (**8**

Scheme 1



a) TBDMSCl, ImH, DMF, rt, overnight, 98% (**6**) or $Me_2C{=}CH_2$, *conc.*-H_2SO_4, CH_2Cl_2, rt, 2 days, 83% (**7**) b) DIBAL, Et_2O-C_6H_{14}, -78°C, 20 min, 82% (**8**) or 30 min, 73% (**9**) c) $DAMNH_2$ or $BnNH_2$, anhyd. $MgSO_4$, PhMe, 0°C, 50 min (**10a**) or 1 h (**10b-d**) (see **Table 1**) d) $BnOCH_2COCl$ (1.3 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, rt, overnight (see **Table 1**) e) HCl, *i*-PrOH, rt, overnight, then 60°C, 3 h (**11a**→**13**), 50°C, 3 h (**11b**→**14**), 40°C, 7 h (**11c**→**13**), or 40°C, 5 h (**11d**→**13**) (see **Table 1**) f) $Cl_3COCOCl$, pyridine, CH_2Cl_2, 0°C, 10 min (**13**→**15**), or 40°C, 4.5 h (**14**→**16**) (see **Table 1**) g) H_2, 10% Pd/C, EtOAc, rt, overnight (see **Table 1**) h) H_2 (5 atom), 5% Rh/Al_2O_3, AcOH, 97%

and **9**) were condensed with di-*p*-anisylmethylamine ($DAMNH_2$) or benzylamine ($BnNH_2$) in the presence of anhydrous magnesium sulfate, giving rise to four types of the chiral imines (**10a-d**). The [2+2]-cycloaddition reactions of **10a-d** with benzyloxylketene *in situ* produced from benzyloxyacetyl chloride in the presence of triethylamine, proceeded in a highly diastereoselective manner, yielding mixtures of the 3,4-*cis*-2-azetidinone derivatives (**11a-d** and **12a-d**) in which the desired diastereomers (**11a-d**) were highly predominent.[6,7] As summarized in **Table 1**, the best chemical yield (88%) and diastereoselectivity (15:1) could be realized for the reactions employing **10a** and **10d** as chiral imines, respectively. Considering the chemical yields of the later synthetic stages as well as the chemical yield and diastereoselectivity of the [2+2]-cycloaddition reaction, the reaction of **10a** with benzyloxyketene seems to be most practical. Stereochemistries of **11a-d** and **12a-d** could be definitely assigned by their ^{1}H-NMR spectra[9] in addition to successful syntheses of **2** from **11a-d** (*vide infra*)[11]

Elaboration of the major products (**11a-d**) to **2** could be achieved in 4 steps. Thus, treatments of **11a,c** with acidic isopropanol (*i*-PrOH) cleanly effected simultaneous alcoholysis of the 2-azetidinone moieties and removals of the TBDMS or the *t*-Bu group and the DAM groups, affording the same isopropyl ester (**13**).[6] It is noteworthy that the DAM group could be readily cleft under the simple acidic conditions. When **11b,d** were subjected to the same conditions as employed for **11a,c**, the isopropyl ester (**14**) could be produced without cleavage of the N-benzyl group. In order to

Table 1 Chemical Yields of Imine Formation (**8** or **9**→**10**), [2+2]-Cycloaddition (**10**→**11** and **12**), Alcoholysis (**11**→**13** or **14**), 2-Oxazolidone Formation (**13**→**15** or **14**→**16**), and Hydrogenolysis (**15** or **16**→**17**)[a)]

	R^2	R^3	Yield (%)				
			8 or **9**→**10**	**10**→**11** and **12** (11:12)	**11**→**13** or **14**[d)]	**13**→**15** or **14**→**16**[d)]	**15** or **16**→**17**
a	TBDMS	DAM	100	88 (10:1)[b)]	84 (**13**)[e)]	90 (**15**)	94
b	TBDMS	Bn	100	59 (12:1)[b)]	86 (**14**)[e)]	64 (**16**)	81
c	*t*-Bu	DAM	100	77 (9:1)[c)]	59 (**13**)[f)]	———	———
d	*t*-Bu	Bn	98	62 (15:1)[c)]	69 (**14**)[f)]	———	———

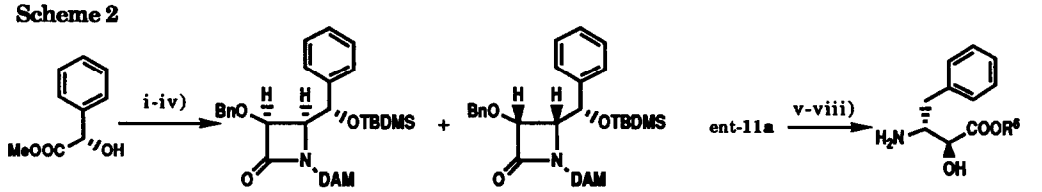
a) The reaction conditions are given in the footnotes of **Scheme 1**. b) Determined by weighing separated **11** and **12**. c) Determined by the ^{1}H-NMR spectrum of the mixture of **11** and **12**. Separation of **11** and **12** could not be achieved. d) Numbers in parentheses indicate the compound numbers. e) A pure sample of **11** was used for the reaction. f) A mixture of **11** and **12** was directly used for the reaction. The yield was calculated based on the total amount of the mixture.

remove the benzylic hydroxyl groups derived from **5**, two sorts of the isopropyl esters (**13** and **14**) were converted to the 2-oxazolidone derivatives (**15** and **16**)[6)] by treating with trichloromethyl chloroformate (phosgen dimer) in the presence of pyridine. Hydrogenolyses of **15** and **16** over 10% Pd on charcoal afforded same isopropyl (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyrate (**17**).[6)] The convergent syntheses of **17** could nicely correlate the stereochemistries of **11a-d**. Further catalytic reduction of **17** over 5% Rh on alumina furnished optically pure **2**, mp 86-86.5°C and $[\alpha]_D^{20}$ -22.0° (c=1.18, $CHCl_3$) [*lit.*,[3c)] mp 86-87°C and $[\alpha]_D^{20}$ -22.0° (c=1.08, $CHCl_3$)].

With completion of the synthesis of **2** from **5**, the explored synthetic route was next applied to ent-**5** to prepare **4**. Thus, as shown in **Scheme 2**, a mixture of ent-**11a** and ent-**12a** (8:1) could be prepared similarly from ent-**5** in 4 steps. A combination of TBDMS and DAM groups was employed to obtain a higher yield in the [2+2]-cycloaddition reaction. Elaboration of ent-**11a** to ent-**17** according to the same procedure as discribed above gave ent-**17**. Acidic hydrolysis of ent-**17** followed by treatment with an ion exchange resin, afforded **4**, mp 235-237°C (decomp.) and $[\alpha]_D^{20}$ +29.9° (c=0.214, 1M HCl) [*lit.*,[4)] mp 219-221°C and $[\alpha]_D^{20}$ +27.9° (c=0.717, 1M HCl)].[12)]

As mentioned above, we have succeeded in exploring a novel synthetic route to antipodal **2** and **4**. The best combined yields (overall 8 steps) of **2** and **4** from **5** and ent-**5** by way of **11a** and ent-**11a** can be calculated as 44% and 30%, respectively. Taking into account high diastereoselectivity observed for the [2+2]-cycloaddition reaction, expeditious elaboration of **11** or ent-**11** to **2** or **4**, and use of com-

Scheme 2



ent-5 ent-11a ent-12a ent-17: R^6=*i*-Pr 4: R^6=H

a) For reaction conditions [steps i)-vii)], see footnotes of **Scheme 1**. i) 93% ii) 80% iii) 100% iv) 90% (ent-**11a**:ent-**12a** = 8:1) v) 70% vi) 93% vii) 92% viii) 6M HCl, 100°C, 4h, then ion exchange resin (AG 50 X W2, H^+-form), 85%

mercially available **5** or ent-**5** as a starting material, the overall process may have potential as one of the most reliable synthetic methods for preparing the (2*R*,3*S*)- and (2*S*,3*R*)-3-amino-2-hydroxycarboxylic acid derivatives such as **2** and **4**.

References and Notes

1) Present Address: Department of Chemistry, Faculty of Science, Kyushu University, Fukuoka 812, Japan.

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3) For other syntheses of **2**, see, a) T. Kamijo, H. Harada, A. Tsubaki, T. Yamaguchi, A. Iyobe, K. Iizuka, and Y. Kiso, *Japan Kokai Tokkyo Koho, JP* 1-172365 (1989). b) H. Harada, A. Tsubaki, T. Kamijo, K. Iizuka, and Y. Kiso, *Chem. Pharm. Bull.*, **37**, 2570 (1989). c) Y. Ito, T. Kamijo, H. Harada, and S. Terashima, *Heterocycles*, **30**, 299 (1990). d) F. Matsuda, T. Matsumoto, M. Ohsaki, Y. Ito, and S. Terashima, *Chemistry Lett.*, submitted for publication.

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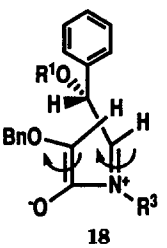
6) Representative physical data of the synthetic intermediates are as follows. **6**: mp 40-41°C, $[\alpha]_D^{20}$ -50.0° (c=1.04, $CHCl_3$); **8**: oil; **10a**: caramel; **11a**: caramel, $[\alpha]_D^{20}$ +32.4° (c=1.11, $CHCl_3$); **12a**: mp 96-97°C, $[\alpha]_D^{20}$ +2.5° (c=1.22, $CHCl_3$); **13**: oil; **15**: oil, $[\alpha]_D^{20}$ +99.7° (c=1.62, $CHCl_3$); **17**: mp 112.5-113°C, $[\alpha]_D^{20}$ -32.7° (c=1.04, $CHCl_3$).

7) The precise reaction mechanism which may rationalize the preferential formations of **11a-d** is quite ambiguous. However, as previously suggested for the similar [2+2]-cycloaddition reaction,[8] the observed results may be accounted for by initial formation of the zwitter-ionic intermediates (**18**) from **10a-d** and benzyloxyketene and subsequent conrotatory ring closure to the indicated direction under an influence of the adjacent chiral center.



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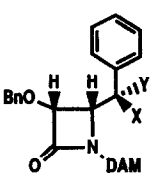
8) a) H. G. Holden, "*Chemistry and Biochemistry of β-Lactam Antibiotics*," Vol. 2, ed. R. B. Morin and M. Gorman, Academic Press, Inc., New York-London, p. 114 (1982). b) C. Hubschwerlen and G. Schmidt, *Helv. Chim. Acta*, **66**, 2206 (1983).

9) The coupling constants of the C_3- and C_4-protons in the 2-azetidinone rings of **11a-d** and **12a-d** were found to be 4.9-5.3 Hz. Since $C_{3,4}$-*trans*-2-azetidinone derivatives regularly exhibit $J_{3,4}$ = ~2.5 Hz,[10] these spectral characteristics clearly suggest that both **11a-d** and **12a-d** bears the $C_{3,4}$-*cis* stereochemistries.

10) Y. Ito, Y. Kobayashi, T. Kawabata, M. Takase, and S. Terashima, *Tetrahedron*, **45**, 5767 (1989).

11) That both **11a** and **12a** has the $C_{3,4}$-*cis* stereochemistries was further ascertained by the following chemical correlation. Thus, desilylation of **11a** [Bu_4NF, THF, 99%] followed by Swern oxidation of the alcohol (**19**) [$(COCl)_2$-DMSO-Et_3N,CH_2Cl_2, 100%] and reduction of the ketone (**20**) [$NaBH_4$, MeOH-CH_2Cl_2, 87%] gave a mixture of the diastereomeric alcohols (**19** and **21**, **19**:**21**=1:10). The predominantly produced alcohol (**21**),



	X	Y
11a:	OTBDMS	H
19:	OH	H
20:	—O—	
21:	H	OH

$[\alpha]_D^{20}$ +26.1° (c=1.31, $CHCl_3$), was found to be enantiomeric to the alcohol, $[\alpha]_D^{20}$ -26.9° (c=1.20, $CHCl_3$), independently prepared by desilylation of **12a** [Bu_4NF, THF, 71%].

12) The hydrochloride of **4** showed mp 190-192°C (decomp.) [*lit.*,[3d] mp 190°C (decomp.)].

(Received in Japan 5 March 1990)