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CONFORMATIONALLY RESTRICTED P_1-P_1' TRANSITION STATE ANALOGUES. SYNTHESIS OF 1(R), 3(R) [1(S), 2(S)] and 1(S), 3(S) [1(S), 2(S)] 3-[3-CYCLOHEXYL-2-[(BOC)AMINO]-1-HYDROXYPROPYL]-2,2-DIMETHYLCYCLOPROPANE CARBOXYLIC ACIDS

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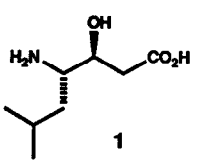
Abstract: A concise synthesis and determination of absolute stereochemistry of two novel diastereomeric cyclopropyl containing transition state mimics is described.

A major advance in the development of renin inhibitors was the replacement of the scissile bond (P_1-P_1') with "transition state mimics" such as statine[1] (**1**) and Leu[CH(OH)CH_2]Val[2a,b] (**2**, LVA). This strategy replaced the P_1-P_1'dipeptide with a nonhydrolysable analogue which contained a β-hydroxyl group thought to mimic a proposed transition state (**3**) in the enzyme- substrate complex.[3] The improved potency and associated specificity of peptides containing transition state analogues (TSA's) has resulted in intense interest in this area of research with the hope of discovering smaller, more potent peptides with improved bioavailability.[4]

Interest in our laboratory has focused on the evaluation of novel TSA's which represent conformationally restricted P_1-P_1' mimics.[5] It is well recognized that the conformational properties of peptides are intrinsically related to their biological activities. The conformational properties of a peptide should relate to its receptor affinity and selectivity, biological transduction (ground state to excited state) and dissociation from the receptor. Through the incorporation of small carbocycles in the transition state insert (see **4**) torsional angles within P_1-P_1' can be expected to influence conformation in both isolated segments, as well as the entire peptide backbone.



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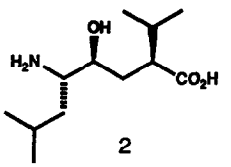

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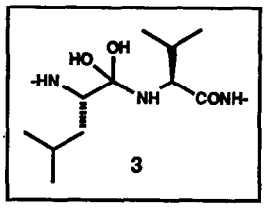

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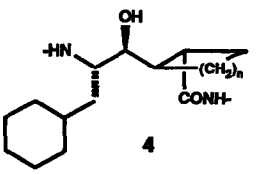

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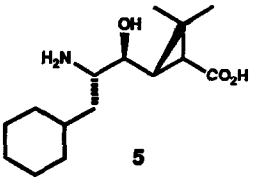

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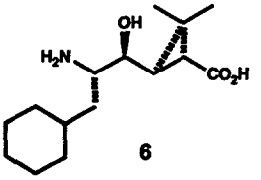


6

Molecular modeling studies established the suitability of the diastereomeric cyclopropyl amino acids **5** and **6** as synthetic targets useful as probes for both local (P_1-P_1') and backbone perturbations on the system.[6]

In this letter we report the synthesis and establish the absolute stereochemistry of two novel diastereomeric transition state analogues containing a cyclopropane ring system.

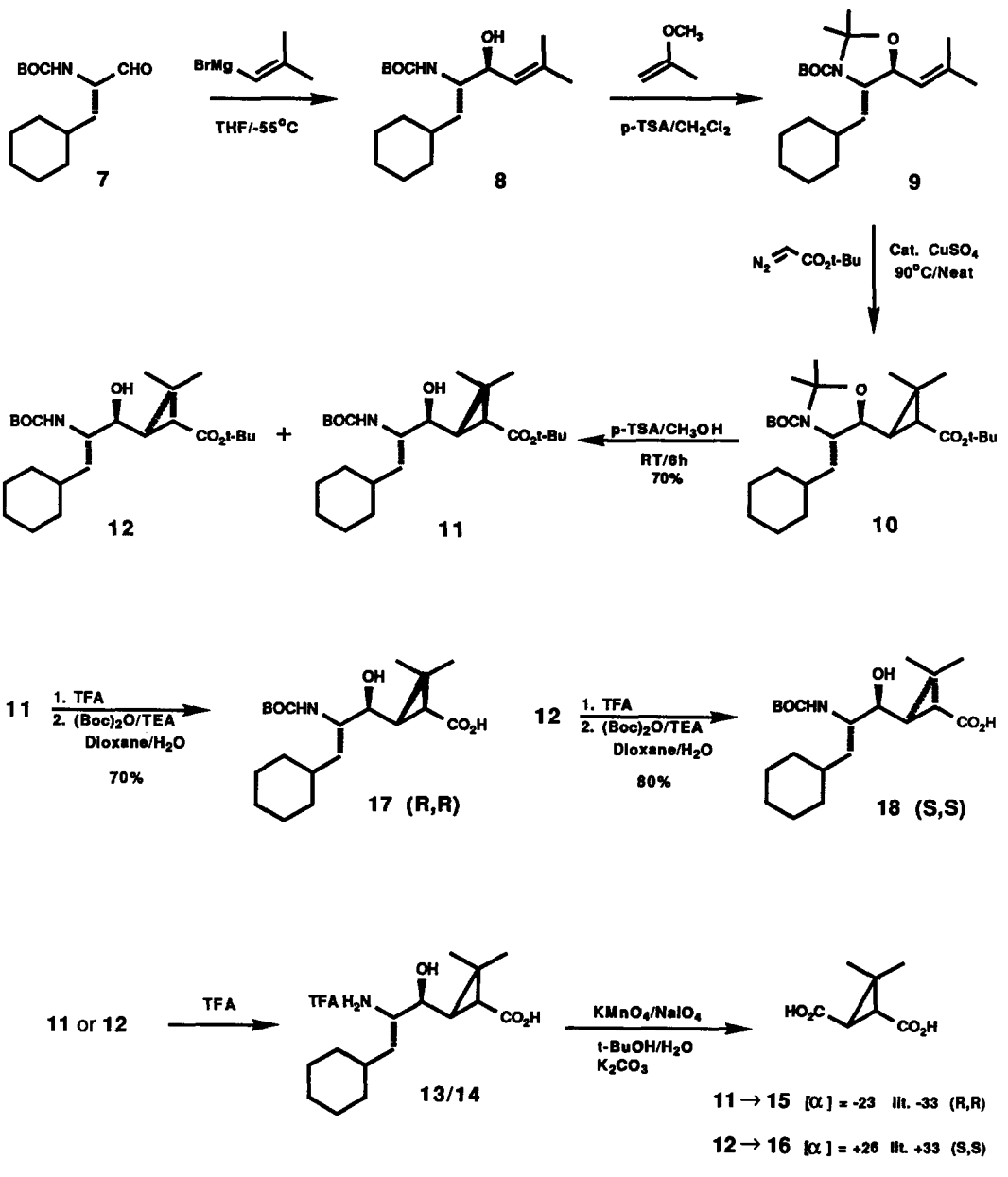
Our approach to the TSA's **5** and **6** involved the cyclopropanation of an amino acid derived olefin (**9**) with the carbene derived from t-butyl diazoacetate.[7,8] Olefin **9** (4S,5S) is readily available from (L)- phenyl alaninol in several steps via aldehyde **7** (see Scheme).[2b] Addition of **7** to 2-methylpropyl magnesium bromide (THF/-55°C) gave **8**[9] as an inseparable mixture (5/1) of diastereomeric amino alcohols in which the threo isomer (shown) predominated. While attempts to add the diazoester directly to **8** or silyl protected derivatives thereof failed, successful cyclopropanation was realized with an acetonide derivative. Treatment of **8** with 2-methoxypropene (PPTS/CH_2Cl_2) afforded **9** in 50% yield from **7**. With **9** in hand we began to investigate cyclopropanation conditions which would allow us to use excess diazo ester rather than excess olefin (the more expensive reactant), as is normally the case.[10] After extensive experimentation with various catalyst and reaction conditions, we found that cyclopropanation of **9** could readily be achieved with an excess of t-butyl diazoacetate (5 eq) in the presence of catalytic $CuSO_4$ (1 mole %/neat/90°C). That reaction afforded **10** as a mixture of facial diastereomers in 44% yield.[11] Treatment of that mixture with acid (0.2 eq. TSA/CH_3OH) smoothly removed the acetonide protecting group to then afford a separable mixture (1/1; silica gel chromatography) of BOC amino alcohols **11** (MP 94-7°C) and **12** (MP 103-5°C).[12]

The absolute stereochemistry of **11** and **12** was then assigned by individual chemical degradation to the know 1,2-cyclopropane dicarboxylic acids (see Scheme). Cyclopropyl ester **11** or **12** was treated with TFA (neat/0°C/RT) to afford the amino acid salt **13** or **14**. Aminols **13** and **14** were oxidatively cleaved[13] with cat. $KMnO_4$/$NaIO_4$ to give the desired diacids **15** or **16** whose absolute configuration has been established.[14] It was then possible to assign the absolute stereochemistry of **11** and **12** based on optical rotations.[15] Thus **11** was assigned the 1(R), 3(R) configuration about the cyclopropane ring and **12** was assigned the 1(S), 3(S) configuration. This facile method of stereochemical assignment should expedite subsequent stereochemical assignments in our evaluation of conformationally restricted TSA's.

To complete the synthesis, both **11** and **12** were first treated with TFA (neat/0°C/RT; which removed both the t-butyl ester and BOC group), then in a second step BOC anhydride (dioxane/H_2O[1:1]/RT) to yield the new protected TSA's **17** (MP 78-82°C)and **18** (MP 118-122°C).

We have devised a concise synthesis of two diastereomeric cyclopropyl containing amino acids for evaluation as transition state mimics. The absolute stereochemistry of these two compounds was established via a novel and efficient degradative procedure. The biological results reflective of the conformational restraints of peptides containing **17** and **18** are in preparation.

SCHEME


BOCHN
CHO
7
BrMg
THF/-55°C
OH
8
OCH3
p-TSA/CH2Cl2
O
BOCN
9
N2
CO2t-Bu
Cat. CuSO4
90°C/Neat
10
p-TSA/CH3OH
RT/6h
70%
11
12
+
1. TFA
2. (Boc)2O/TEA
Dioxane/H2O
70%
17 (R,R)
80%
18 (S,S)
11 or 12
TFA
TFA H2N
13/14
KMnO4/NaIO4
t-BuOH/H2O
K2CO3
HO2C
11 → 15 [α] = -23 lit. -33 (R,R)
12 → 16 [α] = +26 lit. +33 (S,S)

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References and Notes

1. Boger, J.; Lohr, N.S.; Ulm, E.H.; Poe, M.; Blaine, E.H.; Fanelli, G.M.; Lin, T.-Y.; Payne, L.S.; Schorn, T.W.; LaMont, B.I.; Vassil, T.C.; Stabilito, I.I.; Veber, D.F.; Rich, D.H.; Bopari, A.S.; Nature (London) (1983) **303**, 81.
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4. Rich, D.H. In A.J. Barrett and G. Salvesen (eds.) Proteinase Inhibitors, Elsevier, Amsterdam (1986) pp. 179-208. Szelke, M. In V. Kostka (ed.) Aspartic Proteinases and Their Inhibitors, Walter de Gruyter, Berlin (1985) pp. 421-441. Wolfenden, R. Transition States of Biochemical Processes; Gandour, R.D.; Schowen, R.L.; Eds.; Plenum, New York, 1978, p 555.
5. For earlier examples that lack the critical 3S hydroxyl group see: Spaltenstein, A.; Carpino, P.; Miyake, F.; Hyskins, P.B.; Tetrahedron Let. (1986) 2095 and Johnson, R.L.; J. Med. Chem. (1984) **27**, 1351. Also see: Kempf, D.J.; de Lara, E.; Stein, H.H.; Cohen, J.; Plattner, J.J.; J. Med. Chem. (1987) **30**, 1978.
6. Hruby, V.J.; Trends in Pharmaceutical Science (1985) 259. The advantage of the cyclohexyl group over the isopropyl has been discussed (see ref. 2, 3).
7. For a recent review of cyclopropanations with diazoesters see: Maas, G.Topics in Curr. Chem. (1987), **137**, 75.
8. For the synthesis of t-butyl diazoacetate see Org. Syntheses (1968),**48**, 36.
9. All new compounds exhibited physical and analytical characteristics (IR, UV, ^{1}H-NMR/^{13}C-NMR, CHN analysis and/or high resolution mass determination) consistant with the assigned strucuture.
10. For an exception see: Doyle, M.P.; Van Leusen, D.; Tamblyn, W.H. Synthesis (1981), 781. This modification failed with our olefin.
11. Cyclopropanes **10** were a mixture of both facial isomers in both the threo and the erythro series with predominently trans stereochemistry about the cyclopropane ring.
12. Any cis isomers in this mixture were lactonized under the reaction conditions, allowing their easy separation by flash chromatography along with the erythro isomers.
13. Von Rudloff, E. Can. J. Chem. (1965), **43**, 1784.
14. Crombie, L.; Doherty, C.F.; Pattenden, G. J. Chem. Soc. (C) (1970), 1076.
15. Our observed [α]'s were somewhat lower than the literature values for two reasons: 1) The EE of the starting L-phenyl alaninol (commerically available) was 92%, thus the maximum value of [α] was 30, and 2) the cyclopropane dicarboxylic acids contained small amounts of impurities and since the direction of rotation answered our question, we did not purify to analytical purity.

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