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Synthesis and Structure Determination of (3S, 5S)-2,3,5,6-Tetrahydro-3,5-dialkyl-N-(*tert*-butyloxycarbonyl)-4H-1,4-oxazine-2-ones

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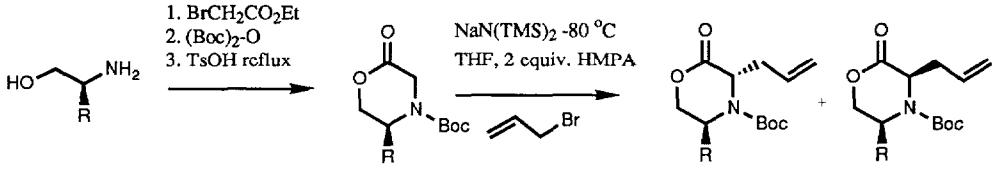
Key words: Stereoselective alkylation; (3S,5S)-2,3,5,6-Tetrahydro-3,5-dialkyl-N-(tert-butyloxycarbonyl)-4H-1,4-oxazine-2-ones

Abstract: (5S)-2,3,5,6-Tetrahydro-5-alkyl-N-(tert-butyloxycarbonyl)-4H-1,4-oxazine-2-ones, which are readily prepared from optically pure 2-amino alcohols alkylate selectively at the C-3 position to give (3S, 5S)-dialkyl-2,3,5,6-tetrahydro-5-alkyl-N-(tert-butyloxycarbonyl)-4H-1,4-oxazine-2-ones in good yield. The structures of compounds ***3e, 5c, 5g , 6h,*** *and* ***5h*** *(p-bromobenzoate) were determined by single crystal X-ray analysis. The structure of* ***5b*** *was determined by conversion to optically active diols* ***6*** *and* ***7*** *and the structure of* ***5f*** *was determined by correlation to* ***5c****.*

Optically active 5,6-diphenyl and 5-phenyl-1,4-oxazine-2-ones have been employed as chiral templates for the synthesis of enantiomerically pure α-amino acids. For example, chiral 1,4-oxazine-2-ones undergo stereoselective electrophilic substitution,[2,3] nucleophlic alkylation,[4-7] and aldol condensation[8] at the C-3 position. The resulting alkylated lactones have the C-3 substituent anti to the C-5 phenyl group. The origin of the diastereoselectively in the alkylation reaction resided in the conformational preference for the C-5 phenyl group to have an axial orientation due to pseudoallylic strain[9], thereby directing the approach of the electrophile to the less hindered face of the enolate, anti to the C-5 phenyl group. We have found that other C-5 substituents can impart diastereoselectively in the alkylation of 1,4-oxazine-2-ones. In this paper we wish to report our results on the stereoselective alkylation of 5-substituted 1,4-oxazine-2-ones.

Optically active 5-alkyl-N-*tert*-butoxycarbonyl-1,4-oxazines-2-ones (**2a-e**) were conveniently prepared in good overall yield and without isolation of intermediates by the reaction of optically active 2-amino alcohols with ethyl bromoacetate, triethylamine at 0 °C to rt, di-*tert*-butyl dicarbonate, and cyclization of the resultant hydroxy ester with p-toluenesulfonic acid monohydrate.[10] The diastereoselectivity of the alkylation reaction was probed by trapping the enolate derived from **2a-e** with allyl bromide and analyzing the crude reaction mixtures using ^{1}H NMR (500 mHz, DMSO). Thus, lactones **2 a-e** were allowed to react with one equivalent sodium hexamethyldisilazide in THF and two equivalents of HMPA at -80 or -60 °C[5] and addition of allyl bromide afforded the C-3 allylated compounds **3 a-e** and **4a-e** in the yields and ratios shown in table 1. Purified lactone **3e** was epimerized by resubmition to the reaction conditions. Comparison of the TLC and ^{1}H NMR of the crude lactone **3e** obtained from the alkylation reaction to the mixture of diastereomeric lactones **3e** and **4e** obtained from the epimerization experiment showed that no diastereomer **4e** was present in the crude alkylation reaction mixture. The alkylation of oxazine-2-ones **2a-e** produced only one major C-3 diastereomer and, by analogy to literature examples,[6,7] we concluded that the alkylation products had the 3S or anti stereochemistry. The products and yields derived from the alkylation of lactone **2e** with various electrophiles are shown in table 2. Reaction of the enolate with benzaldehyde (entry h) produced approximately equal amounts of both anti and syn aldol products. No stereoselectivity was observed at C-3 for the aldol reaction.[11]

Table 1. Synthesis and Alkylation of (5S) 2,3,5,6 Tetrahydro-5-alkyl-N-(*tert*-butoxycarbonyl)-4H-1,4-oxazine-2-ones.

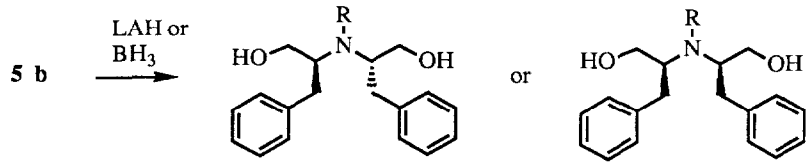


1a-e **2 a-e** **3 a-e** **4 a-e**

R	2 yield, % [a]	2 mp, °C	2 $[\alpha]^{25}_D$ [b]	3 yield, % [a]	Ratio **3**:**4** [h]
a. CH_3	30	85-86	+6.96[c]	88	25 : 1
b. $CH(CH_3)_2$	66	38-40	-30.55[d]	88	14 : 1
c. n-Butyl	45	oil	+3.45[e]	70	26 : 1
d. CH_2-cyclohexyl	55	73-74	+1.09[f]	57	28 : 1
e. $CH_2C_6H_5$	67	95-96	-13.7 g	71	100 : 0

[a] Isolated yields are reported and all compounds passed C, H, N analysis. [b] Specific rotations were measured in chloroform solutions and concentrations were as follows; [c] 2.21, [d] 3.22, [e] 2.95, [f] 0.82, [g] 2.45. [h] The ratios of **3** and **4** were determined by ^{1}H NMR (500 MHz, DMSO) integration of the t-Boc group of the crude alkylation reaction mixture.

Assignment of the C-3 stereochemistry for compounds **3e**, **5c**, **5g**, **5h**, and **6h** was accomplished by single crystal X-ray analysis.[12] For lactones **5b** and **5f**, the stereochemistry was determined by chemical reduction. Reduction of **5b** with either LAH or BH_3 gave the optically active diols **6** ($[\alpha]^{25}_D$ -34.18° (c 1.17, $CHCl_3$) and **7** ($[\alpha]^{25}_D$ -86.03° (c 0.63, $CHCl_3$) in 86% and 89% yield, respectively. Since the diols were optically active, the absolute stereochemistry of **5b** was 3S, 5S. Reduction of the 3R or syn diastereomer **6b**, would have produced the meso compounds **8** and **9**.



optically active

6 R = CH_3
7 R = Boc

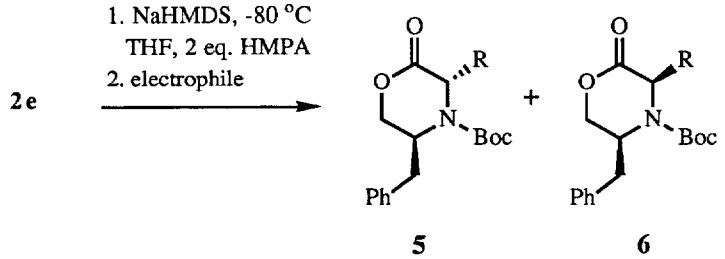
meso

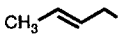
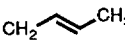
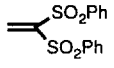
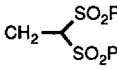
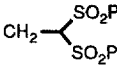
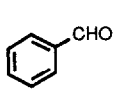
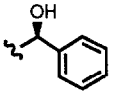
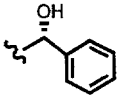
8 R = CH_3
9 R = Boc

Hydrogenation of the crotyl side chain of **5f** (methanol, Pd/C, 4 atm) gave the C-3 butyl lactone which was identical to **5c** by TLC and ^{1}H NMR comparison.

In conclusion, we have demonstrated that the alkylation of 2,3,5,6-tetrahydro-5S-alkyl-N-(tert-butoxycarbonyl)-4H-1,4-oxazine-2-ones produced only the anti (3S) diastereomer at the C-3 position. The selectivity of the alkylation reaction was controlled by the stereochemistry rather than the steric bulk of the C-5 substituent. Application of this methodology for the synthesis of enzyme inhibitors is disclosed in the following paper.

Table 2. Alkylation of (5S) 2,3,5,6-Tetrahydro-5-benzyl-N-(*tert*-butoxycarbonyl)-4H-1,4-oxazine-2-one with Various Electrophiles.



entry	electrophile	**5** R (yield%)[a]	**6** R (yield%)[a]
a.	CH_3I	CH_3 (71)	
b.	$PhCH_2Br$	CH_2Ph (60)	
c.	n-Bu-I	$CH_2(CH_2)_2CH_3$ (64)[b,c]	
d.	$PhCH_2CH_2I$	CH_2CH_2Ph (13)[c]	
e.	$Cl(CH_2)_2CH_2I$	$CH_2CH_2CH_2Cl$ (49)[c]	
f.		 (79)[d]	
g.		 (56)[b]	 (2)
h.		 (26)[e]	 (38)[b]

[a] Isolated yields are reported. [b] Structure determined by single crystal X-ray analysis. [c] Alkylation performed at -60 °C. [d] Structure of **4f** was correlated to **4c** by reduction of the double bond (H_2, methanol, Pd/C, 4 atm). [e] Structure determined by single crystal X-ray analysis of the p-bromobenzoate derivative.

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during the course of this study.

References and Notes

1. Inquires regarding the crystal stuctures should be directed to this author.
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10. **4-(tert-Butoxycarbonyl)-5S-benzyl-2H-1,4-oxazin-2-one (2e).** To solution of 10.0 g (66 mmol) of L-phenylalaninol in 120 mL of dry THF and 16 mL, 11.5 g (114 mmol) triethylamine cooled in an ice-water bath was added 11 mL, 16.5 g (98 mmol) of ethyl bromoacetate (freshly filtered through basic alumina). The reaction mixture was stirred to room temperature over 18 h, recooled in an ice-water bath, and filtered. Remaining solids were washed with cold THF and filtered. Di-*tert*-butyl dicarbonate (20 g, 92 mmol) was added to the combined filterates and the THF was slowly removed under reduced pressure (30 min) at 50-70 °C. The crude residue was dissolved in 300 mL toluene, washed with dilute HCl, saturated sodium bisulfate, dried ($MgSO_4$) and filtered. p-Toluenesulfonic acid monohydrate, 500 mg, was added to the toluene solution and excess toluene (250 mL) was removed by distillation. The toluene solution was cooled, washed with saturated sodium bisulfate, dried ($MgSO_4$) and filtered, total volume 100 mL. Hexane (150 mL) was added and the product crystallized at room temperature to give 10.00 g of a white solid. A second recrystallization gave 1.75 g of a white solid. The mother liquors were purified by flash chromatography using ethyl acetate:hexane (1:4) to give another 1.13 g for a total combined yield of 12.88 g (67%): mp 98-100 °C; $[\alpha]^{25}_D$ = -13.7 ° (c 2.45, $CHCL_3$); IR ($CDCl_3$) 1750 (lactone C=O), 1690 (carbamate C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5H, Ph), 4.35-4.1 (m, 5H, O-CH_2, $COCH_2$ and CH-N), 3.0 (dd, 1H, J = 5 and 12 Hz, CH_2-Ph), 2.82 (dd,1H, J = 10 and 12 Hz, CH_2-Ph), 1.45 (s, 9H, t-butyl); MS (FAB) 291 (M+H); Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.97; H, 7.21; N, 4.81. Found: C, 65.67; H, 7.21; N, 4.75.
11. The di-*n*-butylboron enolate obtained from (5S,6R) 4-(benzyloxycarbonyl)-5,6-diphenyl-2H-1,4-oxazin-2-one on reaction with aldehydes produced the anti aldol product as the major diastereomer, see ref. 7.
12. X-ray crystallographic data for compounds **3e**, **5c**, **5g**, **6h** and **5h** (p-bromobenzoate) are available upon request.

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