Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7339-7342, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01587-2

Asymmetric Synthesis and Absolute Stereochemistry of Cholesterol Absorption Inhibitor, SCH 48461.

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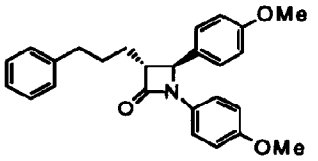
Abstract: The first asymmetric synthesis of cholesterol absorption inhibitor, SCH 48461 is described. The compound was prepared from an asymmetric ester enolate-imine condensation using Oppolzer's chiral ester or the corresponding menthol ester as the stereocontrolling element. From analogy to literature examples, the absolute stereochemistry of the title compound was assigned to be 3*R*, 4*S*.

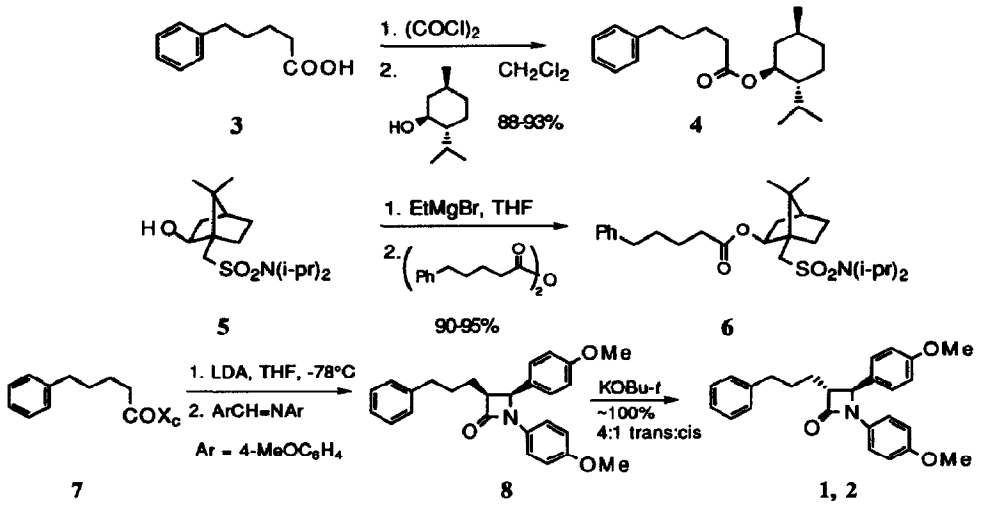
In the course of our work to inhibit the intestinal absorption of cholesterol *in vivo*, we discovered a very potent class of compounds represented by azetidinone, **1**.[1] The racemate of **1** was resolved via chiral chromatography on a Chiralcel OD column into its enantiomers, and the (-) enantiomer, SCH 48461 (**2**), was found to exhibit the desired biological activity. In order to facilitate the development of this derivative, an asymmetric synthesis was required. This work represents the first asymmetric total synthesis and assignment of absolute stereochemistry of this potentially important pharmaceutical agent.



1 (±) SCH 47949
2 (-) SCH 48461

Figure 1. Cholesterol Absorption Inhibitors.

There exists ample literature precedent for the use of the ester enolate-imine condensation in its asymmetric form to prepare enantiomerically enriched azetidinones.[2,3,4] Thus both the D- and L-menthol esters, **4**, of 5-phenyl valeric acid were prepared (see Scheme 1).[5] The D-menthol ester enolate was generated with LDA (1.05 eq) in THF at -78°C and condensed with anisylidine anisidine to give the desired cis β-lactam, **8**, in 64% yield (17:1 ratio of cis to trans). The enantioselectivity was determined to be 66% ee by ^{1}H NMR using chiral shift reagent Eu(tfhc)$_3$.[6] Recrystallization from ether gave racemic crystals of the cis β-lactam and the mother liquor was enriched to 88% ee. No further enhancement of ee in the mother liquor was observed upon repeated recrystallizations. This enriched material could be readily epimerized with KOBu-*t* to give the desired (-) trans β-lactam, **2**, (4:1, trans to cis, 88% ee). This sequence was repeated with the corresponding L-menthol ester to give the opposite enantiomer in comparable yields and selectivity. Addition of HMPA prior to enolate formation, in an attempt to enhance trans selectivity in the condensation, resulted in a complete loss of enantioselectivity. Presumably this result was either due to the loss of chelated transition states in the formation of the cis β-lactam or to a change in mechanism involving ketenes which lack the chiral auxiliary.[2]



Scheme 1. Asymmetric Synthesis of β-Lactams

Table 1. Asymmetric Ester Enolate-Imine Condensation.

X_C	% Yield of **8**	cis:trans	% ee	Major Isomer
D-menthol	64	17:1	66[a]	3*S*, 4*S*
L-menthol	65	24:1	70[b]	3*R*, 4*R*
(-)-isoborneol-10-diisopropyl sulfonamide	55	~18:1	93	3*S*, 4*S*
(+)-isoborneol-10-diisopropyl sulfonamide	50	>36:1	89	3*R*, 4*R*

a. after one recrystallization, mother liquor enriched to 88% ee.
b. after one recrystallization, mother liquor enriched to 84% ee.

In order to enhance the enantioselectivity seen in this condensation, we next examined the use of Oppolzer's chiral auxiliaries as first described by Hart.[3] The chiral alcohol, **5**, was prepared from (+)-10-camphorsulfonyl chloride as described by Oppolzer.[7] The desired ester, **6**, was prepared in 95% yield according to Hart's method by generating the magnesium salt of the alcohol and coupling with the anhydride of 5-phenylvaleric acid.[3] The chiral ester enolate was prepared with LDA at -78°C in THF and was condensed with the requisite imine to give in 45-50% yield the cis β-lactam, **8**. The stereoselectivity in this process was >36:1 cis:trans and 83-86% ee. Unfortunately, the sequence favored the wrong enantiomeric series. This sequence was repeated starting with (-)-10-camphorsulfonyl chloride and generated the correct cis β-lactam, **8**, in 93% ee according to Scheme 1. Epimerization gave a 4:1 separable mixture of the desired trans β-lactam, **2**, and the starting cis β-lactam, **8**, in quantitative yield. Further attempts to enhance the optical purity through crystallization failed. For further biological studies, this material was subsequently purified to enantiomeric homogeneity by preparative chiral chromatography over a Chiralcel OD column.

The absolute sense of asymmetric induction could be determined by comparison of our results with those of Hart in his asymmetric synthesis of antibiotic (+)-PS-5.[3] Starting with (+)-10-camphorsulfonyl chloride, in several steps Hart prepared the butyric acid ester and condensed the corresponding enolate with a cinnamaldimine.[8] Subsequent conversion to (+)-PS-5 confirmed the absolute stereochemistry in the β-lactam product to be 3*R*, 4*R*. By simple analogy to this chemistry, the absolute stereochemistry of our desired cis β-lactam adduct is 3*S*, 4*S* and the absolute stereochemistry of trans β-lactam, **2** (SCH 48461), is 3*R*, 4*S*.[9] The percent ee's that we observed are entirely consistent with those of Hart and may represent the limit of stereoinduction in these simple systems. By extrapolation, we can also relate the absolute sense of stereoinduction observed with the menthol esters. Thus, the D-menthol ester gave predominantly the 3*S*,4*S* stereochemistry as well, although the levels of stereoinduction were significantly less.

Experimental: (3*S*,4*S*)- 1,4-Bis(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone: To LDA prepared from 1.13 mL (1.77 mmol) of *n*-BuLi and 0.26 mL (1.85 mmol) of diisopropylamine in 1.8 mL of dry THF was added 0.735g (1.54 mmol) of the chiral ester, **6**, in 2.2 mL of dry THF keeping the temperature below -65°C. After 45 min. at -78°C, 407 mg (1.69 mmol) of the imine in 3 mL of dry CH_2Cl_2 was added as above. The mixture was stirred at -78°C for 1h; the cold bath was removed, and the mixture was allowed to stir at room temperature for 2h. The reaction was quenched with 100 mL of 1N HCl and extracted with 100 mL of ether. The organic layer was washed with two-75 mL portions of 1N HCl, 50 mL of saturated $NaHSO_3$, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue (0.96g) was chromatographed over ~70g of SiO_2 eluting with 20% ethyl acetate/hexanes to give 473 mg of recovered chiral alcohol (64%) followed by 343 mg (55%) of the desired cis β-lactam. This material was determined to be 93% ee by chiral chromatography.[6]
(3*R*, 4*S*)- 1,4-Bis(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone, 2: The cis β-lactam could readily be epimerized by dissolving in THF (~0.2M concentration) and treating at 0°C with 20 mol% KOBu-*t*. The products were partitioned between 1N HCl and ether. The ether layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The 4:1 mixture of trans and cis β-lactams was chromatographed over SiO_2 eluting with 10% ethyl acetate/hexanes to give the final pure trans β-lactam, **2**, with no enhancement of ee.

Acknowledgments: The help of Dr. M. Puar for the chiral shift reagent ^1H NMR work is greatly appreciated. I am thankful for the encouragement of Drs. J. W. Clader, S. Dugar, and W. Vaccaro during this project. I also wish to acknowledge the efforts of Ms. Mary Ann Caplen in pursuit of this target.

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3. Hart, D. J.; Lee, C.-S.; Pirkle, W. H.; Hyon, M. H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, *108*, 6054-6056.

4. Gluchowski, C.; Cooper, L. Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413-3416.

5. All esters were characterized by ^1H NMR. All final β-lactams were characterized by ^1H and ^{13}C NMR; IR; MS; and CHN analysis. For spectral details of these final products and for epimerization conditions, see reference 1. Cis and trans β-lactam derivatives were distinguished by ^1H NMR coupling constants (J_{cis} = ~6 Hz, J_{trans} = ~2 Hz). Ratios were determined via integration of the appropriate signals from ^1H NMR.

6. Early characterization of % ee's was determined by chiral shift ^1H NMR technology using tris-[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium^{III} (titrated from 0 to ~17 mg Eu reagent per 5 mg of compound in $CDCl_3$) Subsequent analyses were performed on an analytical Chiralcel OD column using 90% hexane/isopropanol at 1.0 mL/min. flow rate. Retention times for the cis enantiomers were 11.8 and 18.4 min. Retention times for the trans enantiomers were 10.2 and 12.7 min. In each case, the first compound off the column represented the "active" series. Although the two methods produced similar results, the superior separation afforded by chiral HPLC made it the method of choice for analysis.

7. Oppolzer, W.; Chaupis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885-5888.

8. Although not specifically stated, Hart used the (+) isomer of camphor sulfonyl chloride in his synthesis of (+)-PS-5. Personal communication from Prof. D. J. Hart.

9. The absolute stereochemistry of 2 was also determined by a different asymmetric synthesis, involving the use of another chiral auxiliary of known configuration. An intermediate in this synthesis containing the auxiliary was subjected to x-ray analysis, further establishing the absolute stereochemistry. Thiruvengadam, T. K. personal communication.

(*Received in USA* 7 *July* 1994; *accepted* 10 *August* 1994)