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Synthesis of an Optically Pure 3-Unsubstituted β-Lactam Using an Asymmetric Reformatsky Reaction and its Conversion to Cholesterol Absorption Inhibitors

B. B. Shankar*, M. P. Kirkup, S. W. McCombie, J. W. Clader, and A. K. Ganguly

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

Abstract: *Asymmetric induction by several chiral alcohols in the reaction of their bromoacetates with imines in the presence of activated Zn (Reformatsky reaction) was studied. Trans-2-phenylcyclohexanol and phenyl menthol gave β-lactam **9**, obtained by cyclizing the diastereoisomeric β-aminoesters **8**, in > 99%ee. The resulting chiral 3-unsubstituted azetidin-2-one **9** was converted to 3-substituted products **11**, **12**, and **13** which exhibit cholesterol absorption inhibitory activity.*

The stereospecific synthesis of the β-lactam **SCH 48461** (Figure 1), a potent cholesterol absorption inhibitor was recently reported.[1] The first synthesis (strategy **I**) involved an asymmetric ester enolate imine condensation followed by base mediated isomerization to the requisite *trans* isomer. A convergent asymmetric synthesis which allows diversity at the 3 position of the β-lactam in a *trans* steroselective fashion would be convenient. Strategy **II** involving the chiral, 3-unsubstituted β-lactam **D** as the central intermediate seemed reasonable. Therefore, the synthesis of **D** or its variant with respect to R_1 and R_2, and its conversion to a variety of analogs of SCH 48461was explored.

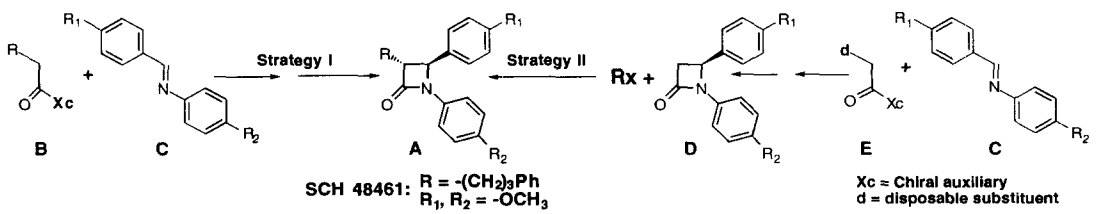


Figure 1

Asymmetric synthesis of a 3-unsubstituted β-lactam:

The synthesis of **D** could be achieved via a chiral α-unsubstituted β-amino acid.[2] There are several reports on enantioselective syntheses of α-substituted β-amino acids including the asymmetric ester enolate-imine condensation,[3] but acetates lacking α-substitution give poor chiral induction.[4] One possible solution would be to have a disposable substituent (**d**), such as - Halogen, -SR or -OR`, which could then be removed after the construction of the β-lactam ring (Figure 1).[5,6] However, this involves an additional step.

The reaction of the zinc enolate of ethyl acetate obtained under Reformatsky conditions with imine **C** to provide 3-unsubstituted β-lactams is well precedented[7] and several variations of this reaction are reported in the literature.[8] Attempts to develop an asymmetric Reformatsky reaction using a chiral imine component have been reported, though the de's were low.[9] The application of this chemistry to bromoacetates of chiral alcohols was considered;[10] our initial, encouraging observations are described in this letter.

Esters (**1-6**) were synthesized in quantitative yields by reacting the Na alkoxides (NaH/THF; -20 °C) of the corresponding chiral alcohols (**i-vi**) with bromoacetyl chloride.

Treatment of a 1:1 mixture of these bromoacetates and imine **7** with activated Zn[11] gave a mixture of diastereoisomeric β-amino esters **8** and traces of β-lactam **9** (Scheme 1). The diastereoisomeric β-amino esters **8** could not be separated by analytical HPLC, and the NMR peaks were not clearly discernible, for quantifying the asymmetric induction.[12] However, the β-amino esters underwent clean cyclization with ethyl magnesium bromide at 0 °C in THF to provide the enantiomeric β-lactams[13] which could be easily seperated on a chiracel AS analytical column.[14] Of the six chiral alcohols studied (-)-*trans* -2-phenylcyclohexanol[15] and (-)-phenyl menthol[16] gave the highest ee's (Table 1). Despite the modest yields, the ready availabilty of the chiral auxiliaries[17,18] and their easy recovery[19] makes this a practical route to chiral 3-unsubstituted β-lactams.

Scheme 1

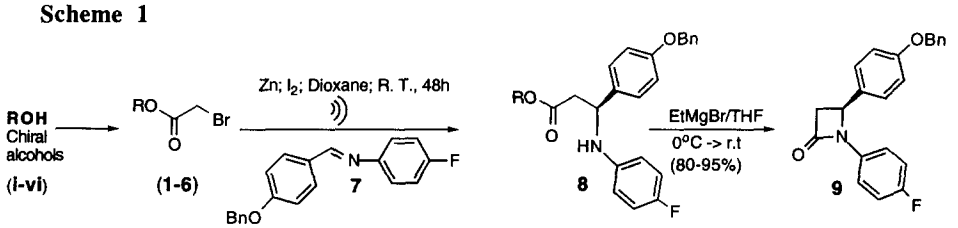
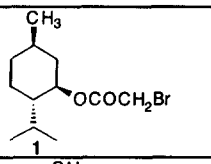
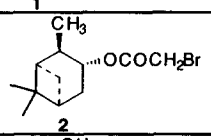
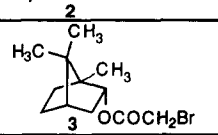
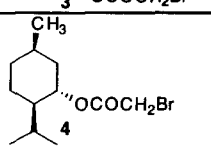
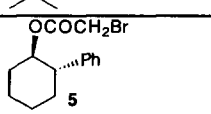
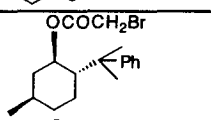


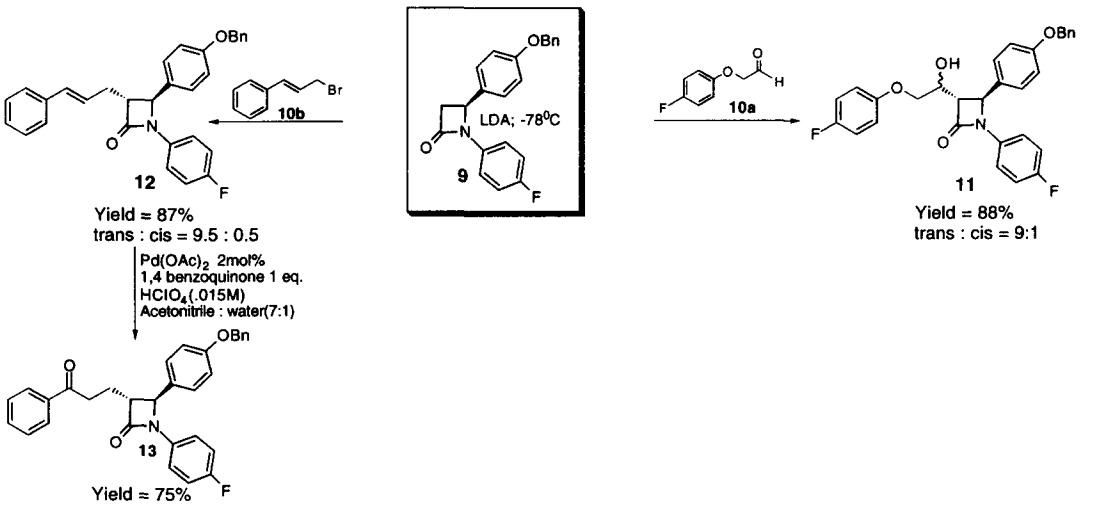
Table 1

Chiral alcohols	Bromoacetates	(#)Yields of β-Aminoesters 8	Enantiomeric ratios of 9
(-)-menthol (**i**)		(**8a**) 70%	60:40
(-)-Isopinocampheol (**ii**)		(**8b**) 60%	70:30
[(1s)-endo]-(-)-Borneol (**iii**)		(**8c**) 55%	60:40
(+)-Isomenthol (**iv**)		(**8d**) 65%	75:25
(-)-trans-2-phenyl-cyclohexanol (**v**)		(**8e**) **45%**	**99:1**
(-)-8-Phenylmenthol (**vi**)		(**8f**) **55%**	**99:1**

Conversion of 3-unsubstituted β-lactam 9 to SCH 48461 analogs:

Lithium enolates of 3-unsubstituted β-lactams react with a variety of electrophiles to provide 3-substituted compounds.[20] Accordingly, the 3-lithio azetidinone was generated from **9** by treatment with LDA at -78 °C and was reacted with aldehyde **10a** to provide the aldol product **11** as an epimeric mixture of alcohols. Allylation of the enolate with cinnamyl bromide cleanly afforded **12**. **12** is potentially useful to access other analogs, as demonstrated by regioselective Wacker oxidation[21] of the double bond to ketone **13** (Scheme 2). In general, the enolate chemistry is stereoselective, favoring *trans* stereochemistry. If required, the *cis* isomer can be readily obtained by a kinetic deprotonation-protonation sequence with LDA at -78 °C followed by an acetic acid quench.

Scheme 2



In summary, we have accomplished a versatile and highly convergent chiral synthesis of SCH 48461 analogs. Their biological evaluation will be published elsewhere.[22]

Acknowledgements: We would like to thank Dr. B. A. McKittrick and Dr. S. Dugar for helpful discussions and suggestions.

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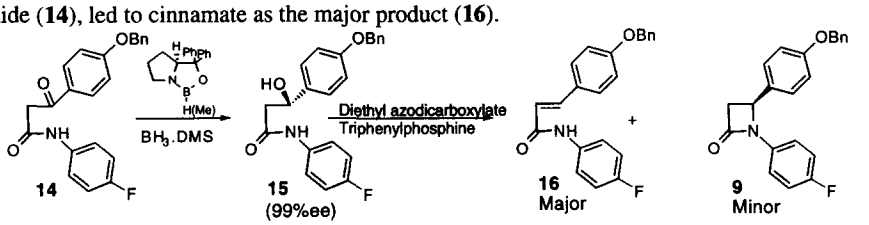
2. Attempts to effect β-lactam formation (**9**) under Mitsunobu conditions from the chiral α-unsubstituted-β-hydroxy amide (**15**) which itself was obtained by efficient chiral oxazoborolidine (Corey, E. J.; Bakshi, R. K.; Shibita, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.) mediated reduction of the corresponding β-ketoamide (**14**), led to cinnamate as the major product (**16**).



3. For a review article on enantioselective synthesis of β-amino acids with recent references see : Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta.* **1994**, *27*, 3.
4. Some recent attempts at solving this problem along with references : (a) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S. *J. Org. Chem.* **1994**, *59*, 8187. (b) Powers, T. S.; Shih, Y.; Wilson, K. J.; Wluff, W.D. *J. Org. Chem.* **1994**, *59*, 6882.
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10. There are numerous reports on the Asymmetric Reformatsky reaction involving α-bromoacetates of chiral alcohols. Reports as early as 1949 (Reid, J. A.; Turner, E. E. *J. Chem. Soc.* **1949**, 3365) and as recent as 1991 (Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, 3417). They all involve carbonyl compounds as the electrophiles (*aldol*) to afford β-hydroxy esters with poor de's.
11. Experimental: Anhydrous dioxane (50 ml) containing commercial Zn dust (2.88 g, 44 mmol) and iodine (0.3g, 1.2 mmol) was refluxed for 1h and then cooled to R. T. The flask was immersed in an ultrrasonication bath, and then a mixture of bromoacetate **5** (7.4 mmol) and imine **7** (1.87 g, 6 mmol) was added, and the mixture was sonicated for 48 h at room temp. Zinc dust was filtered off over celite, and the filtrate was concentrated. The crude product was redissolved in a minimum amount of ethyl acetate and upon standing for 1h most of the unreacted imine (0.3 g) crystallized out and was collected by filtration. The filtrate was concentrated under vacuum and the resulting product was redissolved in a minimum amount of methanol. The major portion of the β-aminoester product **8e** (1.2 g, 2.2 mmol) crystallized out. The mother liquor was concentrated and subjected to silica gel flash chromatography using 10% hexane/ethylacetate as the eluting solvent . This yielded an additional 0.6 g of the β-amino ester.
12. Physicochemical data: **8e:** m.p: 129-131 °C, Anal. Calcd for $C_{34}H_{34}FNO_3$: C, 78.01; H, 6.50; N, 2.67. Found: C, 77.62; H, 6.65; N, 2.74.
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14. Chiral HPLC data: The product was analyzed by chiralcel analytical (25 X 1 cm) HPLC AS column using 20/80 i-Propanol/hexane solvent system. The retention times for the two enantiomers were 15.3 and 16.4 min at 0.5 mL / min flow rate. For pure **9** : $[\alpha]_D$ + 87.8° (c=0.115,$CHCl_3$)
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