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STEREOSELECTIVE SYNTHESIS AND BIOLOGICAL ACTIVITY OF *CIS* AZETIDINONES AS CHOLESTEROL ABSORPTION INHIBITORS

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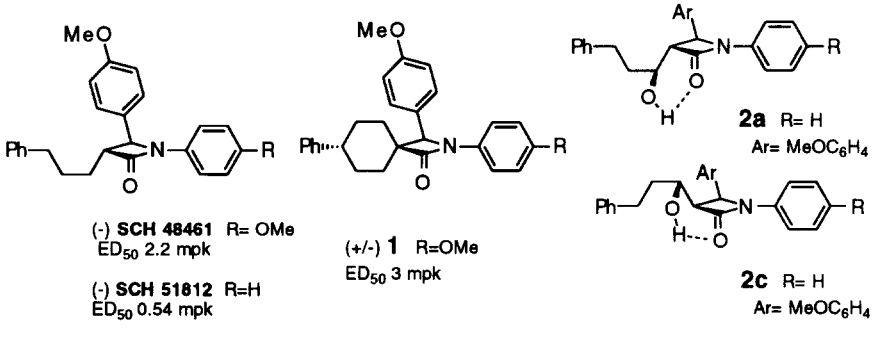
ABSTRACT: The C-3 sidechain of azetidinones related to SCH 48461 was modified by introducing a hydroxyl group at the 1' position. This led to the discovery of the *cis* azetidinone **2c**, which had improved CAI activity. Compound **2c** was prepared using a selective reduction and silane mediated debromination to control the relative stereochemistry of the three centers.

SCH 48461 is a *trans* azetidinone that was recently identified as a potent cholesterol absorption inhibitor (CAI) in the cholesterol-fed hamster[1a] and monkey models.[1b] Initial studies by Burnett et al.[1] demonstrated that both the *trans* and *cis* azetidinones had CAI activity. Subsequent work at Schering led to the discovery of the spirocyclic azetidinone **1**, which also displayed potent CAI activity.[2] The reduced conformational flexibility of **1**, and similar compounds, then served as a model to help define the likely binding conformation of the C-3 phenylpropyl sidechain.[2]

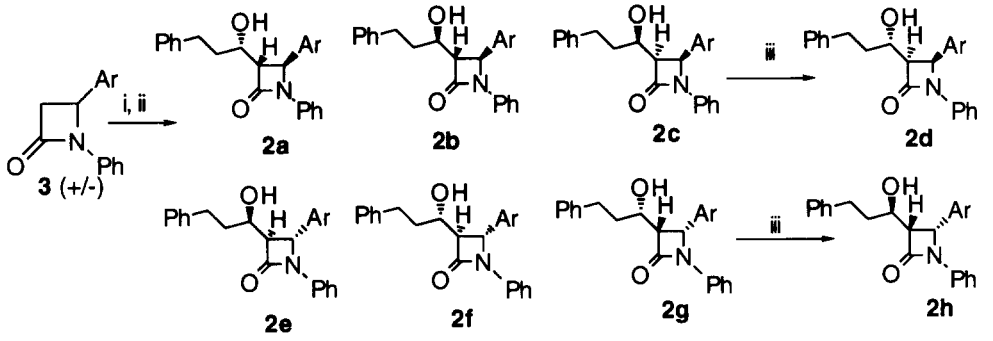
We were interested in preparing compounds such as **2** containing a properly disposed hydroxyl group at the 1' position, since an intramolecular hydrogen bond to the carbonyl oxygen might also have the effect of orienting the side chain in the biologically active conformation.



An aldol reaction of 3-phenylpropanal with racemic azetidinone **3**[3a] afforded a mixture containing racemates of the two *trans* azetidinones and one of the *cis* azetidinones in a 6:3:1 ratio (Scheme 1). Chromatographic separation of the diastereomers and subsequent HPLC resolution provided six of the desired isomers in optically pure form (**2a, 2b, 2c, 2e, 2f, and 2g**).[3b] The remaining *cis* isomers (**2d** and **2h**) were

obtained in good yield by Mitsunobu reactions of **2c** and **2g**, respectively, with formic acid, followed by acidic hydrolysis of the formate esters.[4]

Scheme1



(i) Lithium N-isopropyl cyclohexylamide, RCHO, THF, -78 °C ,y = 88%, (ii) details in ref 3
(iii) a. PPh_3, HCO_2H, DEAD, THF, rt; b. HCl/MeOH, y = 65-70%; Ar = 4-$MeOC_6H_4$.

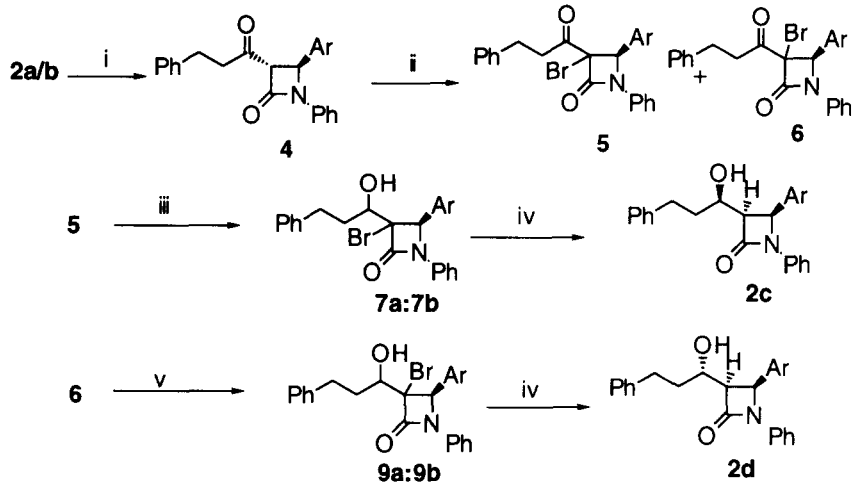
Compounds **2a-h** were tested by oral administration in the cholesterol-fed hamster model[1a] and the results are shown in Table 1. Consistent with earlier findings,[1a,2] there is a strong preference for the S configuration at C-4 (**2a-d** vs. **2e-h**). Comparison of the CAI activity for **2a-d**, with the corresponding deshydroxy analogs indicated that **2a, 2b**, and **2d** were less active; however, the *cis* diastereomer **2c** displayed a 10-fold improvement in CAI activity relative to the deshydroxy analog. This was an interesting finding since it was the first example where the CAI activity of the *cis* azetidinone was greater than that of the corresponding *trans* isomer. The pronounced effect of stereochemistry on activity further supports the idea that the biological target for these compounds is a specific protein involved in cholesterol absorption.[1,2,6]

Table 1. Reduction of cholesterol esters after po administration of compounds (dose given in mg/kg/day)

Compound	**Reduction in liver cholesterol esters**	
	(ED_{50} or % reduction at dose*)	(ED_{50} for des-OH analogs)
2a	8.6	0.54[5a]
2b	1.2	
2c	**0.4**	**4.0**[5b]
2d	0 % @ 3	
2e	38 % @ 10	0 %@ 5[2]
2f	0 % @ 10	
2g	22 % @ 10	0 % @ 10[2]
2h	0 % @ 10	

To develop a diastereoselective synthesis of the *cis* substituted azetidinone **2c**, we envisioned that the previously described borane reduction of magnesium chelated ß-ketoamides[7] could be used to control the stereochemistry of the 1' position. Additionally, we hoped to control the 3,4-azetidinone stereochemistry[8a] by the method of Aimetti[8b] whereby a 3-bromo azetidinone was selectively debrominated using tributyltin hydride. Towards this end, a mixture of *trans* alcohols **2a** and **2b** was oxidized to the ketone **4**, and **4** was brominated with NBS to give the ketones **5** and **6** in a 1:1.3 ratio (Scheme 2).[9] The bromo ketone **5** was reduced with modest selectivity using magnesium trifluoroacetate-*tert*-butylamine borane to give **7a** and **7b** in a 4:1 ratio. Subsequent radical debromination of **7a** using tributyl or triphenyltin hydride gave only poor selectivity for the *cis* azetidinone. Gratifyingly, when the reaction was repeated using tris-(trimethylsilyl)silane,[10] an excellent yield of a 25:1 mixture favoring the desired *cis* isomer **2c** was obtained. A similar sequence on the isomeric bromide **6** provided first the diastereomeric alcohols **9a** and **9b** in a 13:1 ratio, and then debromination of **9a** gave **2d** in a greater than 25:1 *cis*:*trans* ratio.

Scheme 2



(i) PCC/ CH_2Cl_2 ,y = 85%, (ii) NaH/NBS/THF -10 °C, y = 90%, (iii) $Mg(OCOCF_3)_2$, THF, borane-*tert*-butylamine, -78 °C to rt, y = 76%, (iv) $(TMS)_3SiH$ 6 equiv, AIBN-toluene 90 ° C, y = 70-80%, (v) $Mg(OCOCF_3)_2$, CH_2Cl_2, borane-*tert*-butylamine, -78 °C to rt, y = 80%; Ar = 4-$MeOC_6H_4$.

Overlaying the C-3 pendant aryl ring of the most biologically active alcohol **2c** with the rigidified structure **1** indicated that the hydroxyl group of **2c** has the proper orientation (R configuration at 1' position) for the formation of an intramolecular H bond to the amide carbonyl. This is consistent with our hypothesis that the 1' hydroxyl group helps to orient the side chain in a biologically active conformation. However, in the the *trans* series (compounds **2a** and **2b**), the more active isomer **2b** has the R configuration at the 1' position, which does not fit this model. An alternative explanation is that the hydroxyl group in **2c** is correctly positioned to form a hydrogen bond to the, as yet undetermined, biological target. Additional work to further explore the role of the 1' hydroxyl group, and to determine the effect of other sidechain heteroatoms in this series is ongoing and will be reported shortly.

In summary, we prepared eight stereoisomeric 1' hydroxylated azetidinones and determined that the *cis* azetidinone **2c** had improved CAI activity relative to its deshydroxy analog. This represents the first example where a *cis* azetidinone displayed greater activity than the corresponding *trans* isomer. Compounds **2c** and **2d** were prepared from the *trans* ketone **4** using a bromination, reduction and stereoselective silane mediated debromination sequence to control the relative stereochemistry at 3 centers.

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References and notes:

1. (a) Burnett, D. A.; Caplen, M. A.; Davis, H. R. Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733; (b) Salisbury, B. G.; Davis, H. R.; Burrier, R.; Burnett, D. A.; Boykow, G.; Caplen, M. A.; Clemmons, A. L.; Compton, D. S.; Hoos, L. M.; McGregor, D. G.; Schnitzer-Polokoff, R.; Smith, A. A.; Weig, B. C.; Zilli, D. L.; Clader, J. W.; Sybertz, E. J. *Atherosclerosis* **1995**, *115*, 45.
2. Dugar, S.; Clader, J. W.; Chan, T.; Davis, H. *J. Med. Chem.* **1995**, *38*, 4875.
3. (a) **3** was prepared in 70% yield according to Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc. Chem. Comm.* **1984**, *2*, 86. (b) Purification and resolution of **2**: The mixture from the aldol reaction was fractionated by flash chromatography using 85:15 EtOAc:Hex to elute first a mixture of **2** (*trans*) and then **2** (*cis*). HPLC of **2** (*trans*) using SiO_2 followed by Chiralcel OD HPLC using 8:92 IPA:Hex provided **2a, 2e, 2b,** and **2f,** as single enantiomers. **2** (*cis*) was resolved using a Chiralcel OD column with 10:90 IPA:Hex to give **2d** and **2g**. The relative and absolute configuration of **2c** ($[\alpha]_D^{20}$ = - 157.6 °, 2.5 mg/ml MeOH) was assigned based on the X-ray crystallographic structure determination of the brosylate prepared from the enantiomeric alcohol **2g**. The relative stereochemistry of **2b** was established by direct x-ray analysis and the absolute configuration was assigned by comparison of the CD spectra with SCH 48461. c) [θ] values x 10^4 cm^2/dM at 241nm determined as solutions in MeOH: **2a**, -4.6, **2b**,-5.2, **2c**,-5.4, **2d**,-5.6, **2e**,+ 4.5, **2f**, + 4.8, **2g**, + 5.2, **2h**, + 5.8. (coordinates for both X-ray structures have been deposited with Cambridge Crystallographic Data Centre).
4. For a similar transformation see: Tschaen, D. M.; Fuentes, L. M.; Lynch, J. E.; Lasweel, W. L.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *23*, 2779.
5. (a) SCH 51812, single enantiomer. (b) This compound was tested as a racemic mixture and had an IC_{50} of 7.8 mpk. Since our work has shown that the CAI activity resides in the 4-S stereoisomer, the ED_{50} for the single stereoisomer of the deshydroxy analog of **2c** was estimated to be ≥4 mg/kg/day. This estimate was used for the SAR comparison with **2c**.
6. Although the compounds described in this letter were not tested for ACAT inhibitory activity, earlier results[1,11] had demonstrated only weak ACAT activity for a series of structurally related azetidinones. Therefore it is highly unlikely that the weak ACAT activity that these compounds may have would account for the potent CAI activity observed.
7. Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, 103, 6765.
8. (a) Attempted deprotonation/kinetic protonation of **2a/b** (using 2 equiv of LDA followed by AcOH) or **4** (using NaH, followed by AcOH) gave only the recovered *trans* isomers. For additional routes to *cis* azetidinones see: Georg, G. I.; Akgün, E. *Tetrahedron Lett.* **1990**, *23*, 3267, and ref 4.; (b) Aimetti, J. A.; Hamanaka, E. S.; Johnson, D. A.; Kellog, M. S. *Tetrahedron Lett.* **1979**, *48*, 4631
9. The stereochemistry of **5** and **6** was not assigned; **5** eluted first from a SiO_2 column with EtOAc:Hexane, 1:10.
10. Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatglialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267.
11. John W. Clader, Duane A. Burnett, Mary Ann Caplen, Martin S. Domalski, Sundeep Dugar, Wayne Vaccaro, Rosy Sher, Margaret E. Browne, Hongrong Zhao, Robert E. Burrier, Brian Salisbury, and Harry R. Davis, Jr., *J. Med. Chem* 1996 in press.

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