Tetrahedron Letters,Vol.30,No.28,pp 3629-3632,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

DETERMINING THE ABSOLUTE CONFIGURATION OF HINDERED SECONDARY ALCOHOLS - A MODIFIED HOREAU'S METHOD

David E. Barnekow and John H. Cardellina II*
Natural Products Laboratory
Department of Chemistry
Montana State University
Bozeman, MT 59717

Summary - The kinetic resolution of racemic 2-phenylbutyryl chloride by hindered chiral secondary alcohols has been shown to be a viable approach to the determination of the absolute configuration of secondary alcohols through a study of ten chiral alcohols.

For nearly three decades, Horeau's method[1] for determining the stereochemistry of secondary alcohols has been the primary chemical approach to the assignment of absolute configuration. This method, which relies on the kinetic resolution of racemic 2-phenylbutyric anhydride by the chiral secondary alcohol, has twice failed in our studies of chiral sesquiterpene alcohols of marine origin.[2,3] We were successful, however, in defining the stereochemistry of 5-hydroxy-nakafuran-8 (**9**)[2] and neomeranol (**10**)[3] by utilizing 2-phenylbutyryl chloride in place of the anhydride. Reservations expressed by referees in both cases prompted us to examine the use of the acid chloride in greater depth. We report herein a study of the reaction of ten chiral alcohols with both the anhydride[4] and the acid chloride[5] of 2-phenylbutyric acid.

Our intent was to survey a series of secondary alcohols representing a range of steric bulk and conformational rigidity. Trost[6] has recently demonstrated that chiral acid halides can be esterified with little or no racemization; consequently, we anticipated that the alcohols in the study would give similar results with the anhydride and acid chloride, and that the very hindered neopentyl alcohols would react only with the acid chloride. As the summary in Table I reveals, the results, while consistent, were somewhat more complicated.

In every case, the optical rotation of the recovered, unreacted acid[4,5] led to the correct stereochemical assignment, but several classes of alcohol seemed to emerge from this study. The simple, unhindered alcohols (entries **1,3,4**)

Table I

Summary, Comparison of Optical Yields, Acid Anhydride vs Chloride[a]

Entry	Compound	Acid Anhydride optical yield (%)	Acid Anhydride Configuration[c]	Acid Chloride optical yield (%)	Acid Chloride Configuration[c]	Known Configuration[c]
1	2(R)-butanol[b]	10.2	R	2.8	R	R
2	2(S)-octanol[b]	20.5	S	12.6	S	S
3	stigmasterol[b]	64.9	S	2.0	S	S
4	1(R)-phenyl-ethanol[b]	74.5	R	7.0	R	R
5	(-)-menthol[b]	32.1	R	11.3	R	R
6	1(S)-endo-borneol[b]	38.4	S	20.5	S	S
7	brianthein X[7]	23.2	S	35.1	S	S
8	yohimbine[b]	16.0	S	46.7	S	S
9	5-hydroxynaka-furan-8[2]	--	--	7.0	S	S
10	neomeranol[3]	--	--	21.0	R	R

[a] % optical yield calculated with the formula 77.4°n/2N-n for reactions with acid anhydride and 77.4°n/N-n for reactions with acid halide, where n = molar equivalents of secondary alcohol and N = molar equivalents of acid anhydride or acid chloride

[b] commercially available

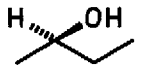
[c] configuration of methine carbon bearing the secondary alcohol

yielded far superior optical yields with the anhydride as reactant. More complex, somewhat more substituted alcohols (entries 2,5,6) resulted in more equitable yields, but still favored the anhydride. As the substitution and steric bulk increased, the acid chloride gave superior yields (entries 7 and 8) or proved to be the only route to product (entries 9 and 10).

The implications would seem clear. Too little differentiation between the large and medium substituents on the chiral alcohol mandates use of the anhydride, where reinforcing steric bulk is available. Conversely, substantial steric bulk and concomitant differentiation between large and medium substituents minimize both the requirement for and reactivity with the anhydride and maximize selectivity for one of the diastereotopic faces of the acid halide. In such cases, the acid halide is a superior or quite possibly the only reagent for the task of stereodifferentiation.

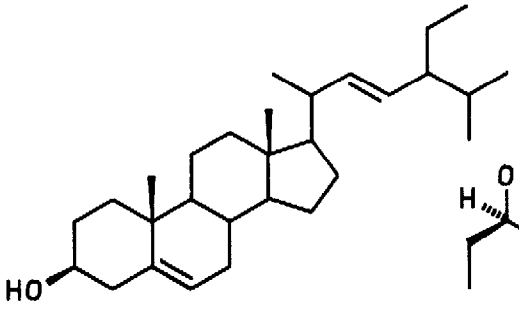
The question of racemization of the acid halide was examined in a series of experiments. The reaction of 2(S)-octanol and (-)-2(R)-phenylbutyryl chloride[5] provided recovered acid with an optical yield of 71%, indicating only 15% racemization. The same acid halide exposed to pyridine or pyridine and 4-dimethylamino-pyridine at 25° and 60° gave reduced optical yields (see Table II).

These results indicate that the chiral acid chloride can be esterified, even under fairly rigorous conditions, with preservation of stereochemistry. These findings, buttressed by Trost's observations[6], indicate that racemization of the acid halide is not a major problem. Horeau's method, therefore, can be extended to include very hindered secondary alcohols.[8]

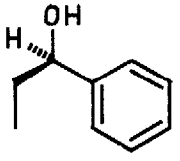


1

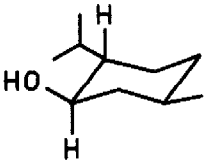
2



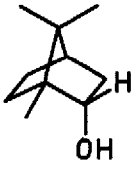
3



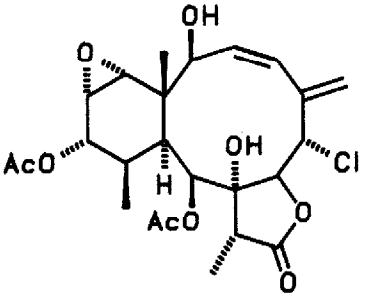
4



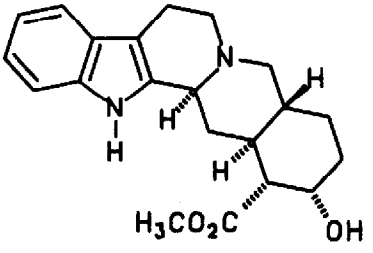
5



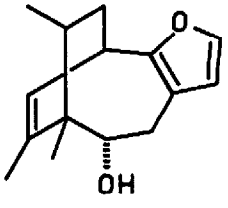
6



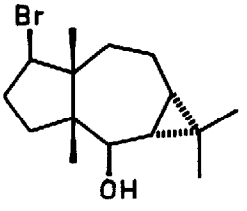
7



8



9



10

Table II

Racemization of (-)-2(R)-Phenylbutyryl Chloride

Entry	Conditions[a]	Optical Yield[b]
1	2(S)-octanol, pyridine, DMAP[c], 60°	71
2	pyridine, DMAP[c], 60°	5.8
3	pyridine, DMAP[c], 25°	42
4	pyridine, 60°	30.3
5	pyridine, 25°	50.2

[a] 4 hours at T indicated, then 16 hours at RT
[b] %
[c] 4-dimethylaminopyridine

References

1. a) A. Horeau, Tetrahedron Lett., 506 (1961); b) A. Horeau, in Stereochemistry, H.B. Kagan, Ed., George Thieme, Stuttgart, 1977, Volume 3, 51.

2. J.H. Cardellina II and D.E. Barnekow, J. Org. Chem., **53**, 882 (1988).

3. D.E. Barnekow and J.H. Cardellina II, J. Am. Chem. Soc., **111**, 3511 (1989).

4. Reaction of the alcohol with racemic 2-phenylbutyric anhydride: To one equivalent of alcohol were added two equivalents of racemic 2-phenyl-butyric anhydride in 2 mL dry pyridine. The mixture was stirred at RT for 20 hours, at which time it was reduced in vacuo, suspended in 50 mL CH_2Cl_2 and washed with 5% $NaHCO_3$ (4 x 20 mL). The CH_2Cl_2 phase was reduced, in vacuo, to give the ester(s); the aqueous phase was acidified (to pH 5) with HCl and extracted with CH_2Cl_2 (4 x 20 mL). Evaporation of this CH_2Cl_2 phase gave the unreacted 2-phenylbutyric acid.

5. Reaction of alcohol with 2-phenylbutyryl chloride: To one equivalent of alcohol were added two equivalents of racemic 2-phenylbutyryl chloride in 2 mL dry pyridine and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at 60° for 4 hours and then allowed to stand at RT for 16 hours. The mixture was then reduced, in vacuo, suspended in 50 mL CH_2Cl_2 and extracted with 5% $NaHCO_3$ (4 x 20 mL). Evaporation of the CH_2Cl_2 phase provided the ester(s). The aqueous phase was acidified (to pH 5) with HCl and extracted with CH_2Cl_2 (4 x 20 mL). Evaporation of this CH_2Cl_2 phase gave the unreacted acid residue.

6. B.M. Trost, J.L. Belletire, S. Godleski, P.G. McDougal, J.M. Balkovec, J.J. Baldwin, M.E. Christy, G.S. Ponticello, S.L. Varga and J.P. Springer, J. Org. Chem., **51**, 2370 (1986).

7. S.H. Grode, T.R. James, Jr., J.H. Cardellina II and K.D. Onan, J. Org. Chem., **48**, 5203 (1983).

8. This work was supported by the Office of Sea Grant, Department of Commerce, and by the state match (MONTS) to an NSF-EPSCOR grant. Taken, in part, from the Ph.D. thesis of D.E. Barnekow, Montana State University, 1989.

(Received in USA 8 March 1989)