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ASYMMETRIC SYNTHESIS *VIA* ACETAL TEMPLATES. 9.[1] FURTHER STUDIES OF THE ALLYLATION REACTION. PREPARATION OF (-)-DIHYDROMYOPORONE

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ABSTRACT: A procedure has been developed for the high-yield coupling of chiral acetals 1 with allyltrimethylsilane (2, R'=H) as well as with methallyltrimethylsilane (2, R'=Me) to afford the hydroxy ethers 3 in which the new chiral center is formed highly enantioselectively. Homoallylic alcohols 4 of high ee are produced by removal of the chiral auxiliary.

The Lewis acid catalyzed reaction of chiral acetals of type 1 with various nucleophiles, e.g., 2 (R'=H), proceeds stereoselectively to give coupling products, e.g., 3a + 3b (R'=H) in which the former diastereomer is predominant.[1,2] Removal of the chiral auxiliary (by oxidation/β-elimination) leads to secondary hydroxylic products, e.g., 4 (R'=H), in good to excellent ee.[1,2] The selectivity of the coupling process depends on (a) the nature of the substituent R in the acetal 1, (b) the structure of the nucleophile, (c) the type of catalyst, and (d) the reaction conditions, i.e., solvent, temperature, concentration and order of addition of reagents. Among the nucleophilic partners that have been examined,[1,2] allyltrimethylsilane (2, R'=H)[2a] has proved to be the most susceptible to variations in the selectivity of the coupling process. As the result of further study we now report on procedural modifications involving the use of a mixed catalyst,[3a,b] $6TiCl_4 \cdot 5Ti(O\textit{i}\text{-}Pr)_4$, which have effected dramatic improvement in selectivity as compared with the results previously reported[2a] for the acetals of entries 1, 2 and 3, Table 1.[4] Compared with 2 (R'=H), methallyltrimethylsilane (2, R'=Me) has proved to be a particularly effective nucleophile which couples with acetals 1 even more selectively (entries 4, 5 and 6, Table 1). In view of the well-established stereochemical course of the coupling reactions of entries 1 and 2, Table 1,[2a] as well as those of related cases,[1,2b,c] the configurations of the products in entries 3-6, Table 1, are presumed to be as shown. That the reaction with the new nucleophile 2 (R'=Me) proceeds in this same stereochemical sense was confirmed in the case of the product 4 (R = cyclohexyl, R'=Me) (entry 5, Table 1) by reduction (H_2/PtO_2/EtOAc), to (-)-cyclohexyl-*i*-butylcarbinol, $[\alpha]_D^{20}$ -30.6° (c 1.87, CCl_4), which is known to have the S configuration.[5] The values for % ee (Table 1) reflect the enantioselectivity of the overall conversion 1 → 4, and the optical purity of 4 is calculated by correcting these values for the % ee of the chiral auxiliary.[6]

The allylation reaction promoted by $TiCl_4$ may proceed *via* a combination of S_N2- and S_N1-like processes.[2d] It is probable that the oxocarbenium ion structure of the S_N1 transition state would have some acyclic character resulting in diminished chiral recognition. A weaker Lewis acid, such as the mixed catalyst described above, should favor the more diastereoselective S_N2 process since the displacement requires greater assistance from the nucleophile.

Scheme 1

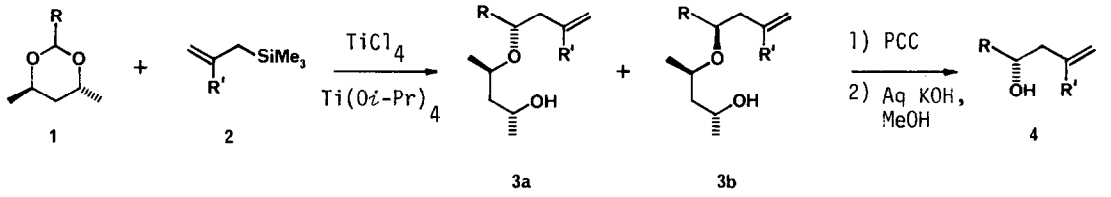


TABLE 1

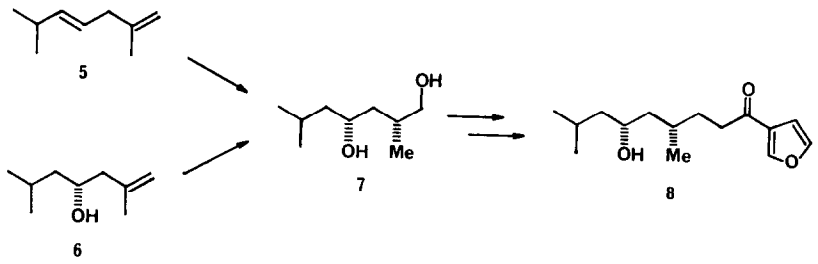
Results of Transformations Shown in Scheme 1

Entry	R	R'	Coupling Product 3		Olefinic Alcohol 4		
			% Yield[8,9]	3a/3b[10]	% Yield[8,9]	% ee[6]	$[\alpha]^{20}D$ CCl_4 (c)
1	*n*-octyl	H	98	98:2	97	96	+10.6° (4.87)
2	3-butenyl	H	92	98:2	84	96	+12.3° (2.00)
3	cyclohexyl	H	98	95:5	94	90	- 0.4° (2.66)[a]
4	*n*-octyl	Me	95	>99:1	98	>98	+11.2° (3.02)
5	cyclohexyl	Me	95	99:1	90	98	+ 3.8° (1.36)
6	*i*-butyl	Me	93	>99:1	96	>98	+28.1° (1.20)

[a] -10° (0.64) in EtOH.

The use of the weaker and more hindered mixed catalyst is not a panacea; for example the allylation of pivalaldehyde acetal 1 (R = *t*-butyl) gives no coupling by the above procedure. Under "standard" conditions with $TiCl_4$[2a] the ratio 3a/3b (R = *t*-butyl, R'=H) was 87:13 (yield,[8] 86%). However, the diastereoselectivity of even this extreme case was subject to improvement: i.e., instilling over 55 min a solution of $TiCl_4$ (0.58 mmol) in CH_2Cl_2 (10 ml) into a solution of the acetal (0.29 mmol) and 2 (R'=H) (2.32 mmol) in CH_2Cl_2 (40 ml) at -78°, afforded in 90% yield 3 (R = *t*-butyl, R'=H),[8,9] 3a/3b = 92:8.[10] This example serves as a warning that it may be necessary to "tailor-make" procedures and one should not be discouraged by a single poor result in a new system.

The availability of alcohol 6 (i.e., 4, R = *i*-butyl, R'=Me, entry 6, Table 1) in >95.5%[6] enantiomeric purity, prompted us to explore its use for the asymmetric synthesis of dihydromyoporone (8),[11] a potato stress metabolite. Still and Darst[12] have described the total synthesis of the racemic form of 8, the critical step being the elegant, highly diastereoselective, intramolecular bis-hydroboration of the diene 5 to yield the syn(±)diol 7. Hydroboration of 6 and of several derivatives showed little syn/anti selectivity. The best result



obtained so far has been with the trifluoroacetate of 6 and thexylborane (3 mol eq./THF/ -78 to -15°C, 17 h; 30% H_2O_2/8 M KOH/EtOH 1:1:2) which gave in 98.5% yield a 76:24 ratio of diols in favor of the syn form 7.[13] Fortunately this diastereomeric mixture was readily and completely separated in a single-pass HPLC (21.2 mm X 2.5 cm DuPont Zorbax O.D.S. column; 3:2 MeOH/H_2O) giving >95%[6] optically pure 7 $[\alpha]_D^{26}$ + 6.3° (c 1, CCl_4). The ^1H and ^{13}C NMR spectral properties of 7 were in complete agreement with those reported[12] for the racemic material. Using a sequence that was essentially the same as Still's,[12] we have converted 7 into dihydromyoporone, $[\alpha]_D^{20}$ -3.6° (c 1.95, MeOH). The ^1H and ^{13}C NMR spectral properties were indistinguishable from those reported[12] for the racemic as well as the natural product. The reported[14] $[\alpha]_D^{25}$ of a specimen of the natural product is -6.4 ± 1.5° (c 1.34, MeOH) which, considering the difficulty of duplicating determinations with small samples having very low rotations, is not in serious disagreement with ours. Since the signs of the rotations are the same we conclude that we have fortuitously produced the natural enantiomer; and that the hitherto unknown absolute configuration of dihydromyoporone is that shown in formula 8.

Acknowledgement. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research. We wish also to thank Professor W. C. Still for providing us with full experimental details for the conversion 7 → 8 in the racemic series, and for copies of the NMR spectra of racemic and natural specimens of 8.

References and Notes

1. Paper 8 in this series: Lindell, S. D.; Elliott, J. D.; Johnson, W. S. Tetrahedron Lett., 1984, in press.

2. (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. J. Am. Chem. Soc., 1983, 105, 2088; (b) Johnson, W. S.; Elliott, R.; Elliott, J. D. ibid., 1983, 105, 2904; (c) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. J. Org. Chem., 1983, 48, 2294; (d) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. Tetrahedron Lett., 1984, 25, 591.

3. (a) Based on the 1:1 catalyst of Mukaiyama, T. Angew. Chem., Int. Ed. Engl., 1977, 16, 817.

(b) The procedure for the coupling reactions listed in Table 1 follows: $Ti(Oi\text{-}Pr)_4$ (0.74 ml, 2.5 mmol) was added to a solution of $TiCl_4$ (0.33 ml, 3.0 mmol) in 9 ml of CH_2Cl_2 under argon. (Note: reversing the order of mixing the components gave a less effective catalyst.) This solution was instilled over ca. 2.25 h via a motorized syringe into a stirred solution of 114 mg (0.50 mmol) of the acetal 1 (R = *n*-octyl)[2a] and 0.63 ml (4.0 mmol) of allyltrimethylsilane in CH_2Cl_2 (2 ml) at -78°C under argon. After an additional 15 min, MeOH (2.5 ml) was added, then the mixture was warmed to >0°C and washed with 1 M hydrochloric acid, water, saturated $NaHCO_3$, water, brine and dried ($MgSO_4$). Chromatography[8] (8:1 pentane/ether) gave 0.132 g of 3a/3b (R = *n*-octyl, R'=H). In the case shown

in entry 3, Table 1, the procedure was modified by diluting the acetal-silane solution in 20 ml CH_2Cl_2/mmol of acetal, and allowing 4 h for addition of catalyst plus 1 h standing at -78°C. Without this modification, the ratio 3a/3b was lower, 93:7 (yield,[8] 93%).

(c) The procedure for the PCC oxidation of the coupling products 3a/3b to the corresponding ketones is unexceptional (see footnote 11 of ref. 2a).

(d) The base-catalyzed β-elimination procedure described previously (footnote 15 of ref. 2a) does not effect racemization of the alcohols 4 so long as the reaction time does not exceed 5 h. After 16 hr 3-4% racemization (probably *via* a carbinol-carbonyl equilibration mechanism, E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Co., New York, 1962, p. 37) was observed in the case of alcohol 4 of entry 3 (Table 1): ee 84% (as compared with 87.6% after 5 h) by the MTPA ester method (ref. 6).

4. These results compare favorably with Brown's method for the asymmetric synthesis of homoallylic alcohols. Brown, H. C. and Jadhav, P. K. J. Am. Chem. Soc., 1983, 105, 2092.

5. Burrows, E. P.; Welch, F. J.; Mosher, H. S. ibid., 1960, 82, 880.

6. The % ee values are derived directly from the ratios of 3a/3b (Table 1). The identity of these ratios with those of the corresponding ketone mixture (ref. 10), obtained by oxidation of 3a/3b with PCC (ref 3c), proves that no epimerization occurs during this step. Since the conditions for the β-elimination of the ketones (to remove the chiral auxiliary) do not effect racemization of the resulting alcohol 4 (ref. 3d), the aforementioned diastereomeric ratios unequivocally reflect the enantioselectivity for the overall conversion 1 to 4 which can be thusly determined *irrespective* of the optical purity of the acetal 1. The optical purities of the alcohols 4 are obtained by correcting the % ee values in Table 1 for the % ee of the R,R-2,4-pentanediol used for making the acetals 1. This latter value was determined by GC (ref. 10) of the bis-MTPA ester (ref. 7) of the diol to be 97.5% for the sample (Aldrich Chem. Co.) used in the present study (Dr. Tai's specimens of the R,R and S,S diols used in earlier work, refs. 2a,2b, proved to be 99.5% ee). Thus the optical purity for alcohol 4 of entry 3 (Table 1) is calculated to be 87.75%. This estimation was confirmed by direct determination of the ee of this alcohol via the MTPA ester method (ref. 7): 87.6%. Since numerous such confirmations have already been made (refs. 1 and 2), we feel that in general the optical purity of asymmetrically synthesized hydroxy compounds via chiral acetals can now be calculated with certainty from the diastereomeric ratio of the coupling products. Thus the ee for 6 and, in turn 7 as well as 8, is estimated to be >95%.

7. Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem., 1969, 34, 2543.

8. The product was submitted to flash chromatography using "Merck silica-gel 60 H for thin layer chromatography."

9. (a) The GC and TLC showed no indication of extraneous components; (b) the ^1H NMR and IR spectra were entirely consistent with the assigned structure, (c) a satisfactory combustion analysis was obtained for an appropriately purified specimen.

10. The diastereomeric ratios of 3a/3b, as well as of the corresponding ketones (obtained by PCC oxidation), and of the MTPA esters (ref. 6) were determined by GC on a 15-m SE-54 capillary column, which showed a base-line separation of the two peaks.

11. Burka, L. T. and Iles, J. Phytochemistry, 1979, 18, 873.

12. Still, W. C. and Darst, K. P. J. Am. Chem. Soc., 1980, 102, 7385.

13. Cf. Evans, D. A.; Bartroli, J.; Godel, T. Tetrahedron Lett., 1982, 4577.

14. Personal communication from Dr. L. T. Burka.

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