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ASYMMETRIC FUNCTIONALIZATION AT A PROCHIRAL CARBON CENTER BY THE AID OF SULFINYL CHIRALITY: A SELECTIVE FORMATION OF 6-SUBSTITUTED (3R,S_S)- AND (3S,S_S)-3-HYDROXYMETHYL-3,4-DIHYDRO-5-(p-TOLYL)SULFINYL-2H-PYRANS

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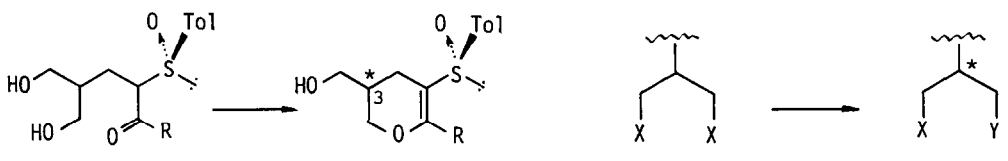
Summary: A successful asymmetric functionalization of prochiral gem-bis(hydroxymethyl) groups has been achieved by the aid of a sulfinyl chirality.

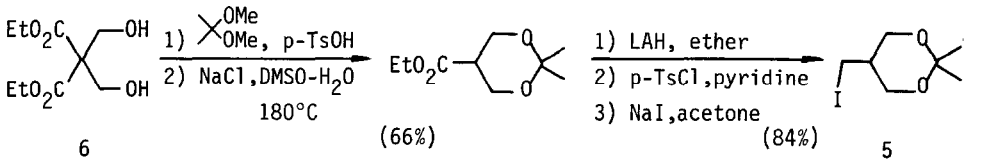
Previously we reported that some simple spiroketals were synthesized with extremely high stereoselection at the spirocarbon center by means of an intramolecular Michael addition reaction of hydroxyl group to the chiral vinyl sulfoxide moiety.[1] Now our synthetic efforts have been directed to the more complex spiroketal natural products, talaromycins,[2] which are equipped with four asymmetric carbon centers. In our plan, an asymmetric induction at the C_3 position of the dihydropyran **1** (R = $CH_2CH_2CH(CH_2OH)_2$) starting from the linear precursor **2** (R = $CH_2CH_2CH(CH_2OH)_2$) is initially required for elaboration of optically active talaromycins. This transformation (**2**→**1**) means an asymmetric functionalization of gem-bis(hydroxymethyl) groups, and is essentially equivalent to the conversion of **3** to **4**. Although such asymmetric transformations are recognized to be very valuable in present synthetic organic chemistry, the successful chemical conversions have been little known to date.[3,4] In this communication we report a novel method for asymmetric induction of prochiral gem-bis(hydroxymethyl) groups illustrated by a selective formation of both (3R)- and (3S)-isomers of the dihydropyrans **1**.



2 **1** **3** **4**

X = OH, COOR' etc.

The prochiral segment **5** neccessary for preparation of **2** was synthesized from the malonate **6**[5] as shown in the following scheme.



6 (66%) (84%) 5

Lithium salt of the optically active sulfoxide **7**[6] was reacted with ethyl acetate in THF at -78°C to afford the keto-sulfoxide **8a** in 89% yield, which was alkylated with **5** in the presence of 18-crown-6 and potassium carbonate to give **9a** in 47% yield.[7] An acidic treatment of **9a** gave the diol **2a** in 88% yield. Although a direct conversion of **2a** to the dihydropyran **1a** was possible by the treatment with p-toluenesulfonic acid in THF, this resulted in non-stereoselection around C_3 chirality of the product, probably due to a long distance between the chiral sulfur center and the prochiral C_3 position. The problem was solved by medium of the dioxabicyclic compound **10.** An intramolecular acetalization of **2a** smoothly proceeded on treatment with zinc chloride in dichloromethane at room temperature. A easily separable diastereomeric mixture of **10a** was obtained 93% yield: (7S)-**10a** [mp 116-117°C, $[\alpha]_D^{23}$ +246.4° (c 0.63, $CHCl_3$)] and (7R)-**10a** [mp 99-100°C, $[\alpha]_D^{23}$ +31.24° (c 0.83, $CHCl_3$)] in 3.6/1 ratio. Stereochemical assignment of each isomer was confirmed on basis of ^{1}H-NMR spectral data.[8] Exposure of the mixture to trifluoroacetic acid (ca. 10 equiv.) in benzene at room temperature followed by hydrolysis gave a mixture of the (3S)- and (3R)-dihydropyrans **1a** (2.7:1) in 78% yield via a regioselective fission of the pro-S C_1-O bond.[9] On the other hand, under the condition of aluminium chloride (ca. 10 equiv.) in THF at room temperature the opposite selectivity was observed ((3S)-**1a**/(3R)-**1a** = 1/2.5 in 89% yield). Detailed experiments have revealed that either (7S)- or (7R)-**10a** gave (3S)-**1a** mainly under the trifluoroacetic acid conditions. By employment of aluminium chloride, (7S)-**10a** afforded (3R)-**1a** predominantly while (7R)-**10a** exhibited non-selectivity (see Table). Reasons for the observed selectivities are under consideration. Structural confirmation of (3S)- and (3R)-**1a** was obtainable from their benzylation. The mixture of (3S)- and (3R)-**1a** given on Run 1 (Table) was benzylated in the usual manner to afford (3S)-**11** (61%) and (3R)-**11** (28%). In ^{1}H-NMR spectra, the latter exhibited a signal of one of the C_3-methylene protons at 3.69 ppm higher than the signals of the former, owing to a shielding effect of the aromatic ring attached at the chiral sulfur atom.[10]

Preparation of the dihydropyran **1b,** a model compound for talaromycins, was next examined. Lithium salt of **7** was allowed to react with ethyl isocapronate[11] to give the keto sulfoxide **8b** (82%), The base-catalyzed alkylation of **8b** with **5** afforded **9b** (46%), which was converted into the diol **2b** (89%). Treatment of **2b** with zinc chloride in dichloromethane gave the dioxaspiro compound **10b** (85%) as an inseparable diastereomeric mixture.

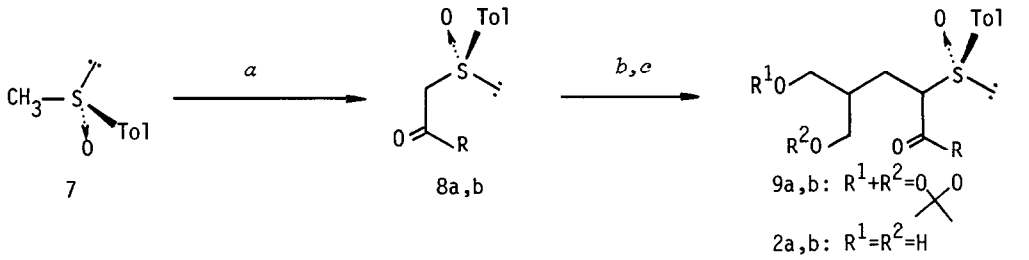
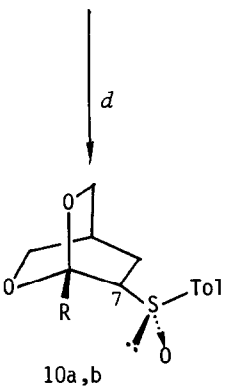


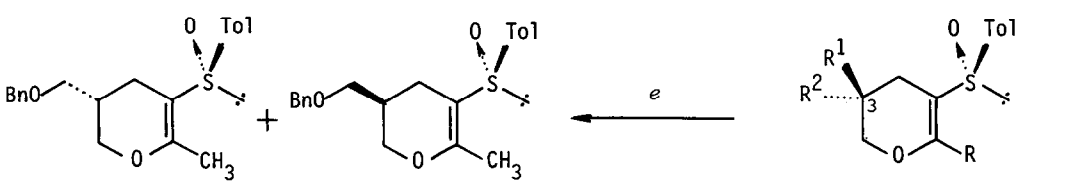
Table. Conversion of 10 to 1

Run	Starting Material	Conditions[a]	Product	Yield[b]	Ratio of (3S)/(3R)[c]
1	10a[d]	A	1a	78	2.7/1
2	(7S)-10a	A	1a	79	2.4/1
3	(7R)-10a	A	1a	76	3.7/1
4	10a[d]	B	1a	89	1/2.5
5	(7S)-10a	B	1a	90	1/2.9
6	(7R)-10a	B	1a	84	1.2/1
7	10b[d]	A	1b	77	2.3/1
8	10b[d]	B	1b	99	1/4.0

a A: CF_3CO_2H (10 eq.) in C_6H_6 at r.t. B: $AlCl_3$ (10 eq.) in THF at r.t. *b* Isolated Yield (%). *c* Calculated by a HPLC analysis. *d* A mixture of (7S)- and (7R)-isomers was used.



Table



Conditions: *a* $LiNEt_2$, THF, -78°C; RCO_2Et, -78°C. *b* 5, K_2CO_3, 18-crown-6, CH_3CN, 40°C. *c* 0.05N HCl, THF, r.t. *d* $ZnCl_2$ (20 eq.), CH_2Cl_2, r.t. *e* NaH, THF, r.t.; Benzyl bromide, r.t.

a: R = Me
b: R = *i*-Am

Treatment of **10b** with trifluoroacetic acid gave a mixture of (3S)- and (3R)-**1b** in 77% yield ((3S)-**1b**/(3R)-**1b** = 2.3/1). The reaction with aluminium chloride also resulted in the reverse stereoselectivity ((3S)-**1b**/(3R)-**1b** = 1/4.0).

Thus, a selective functionalization of prochiral gem-bis(hydroxymethyl) groups has been achieved by means of an indirect 1,4-asymmetric transfer of the sulfinyl chirality. Although the d.e. of the products **1** is not so satisfactory (39 - 60%), the present methodology seems to be very valuable from viewpoint of easy handling of the products, availability of reverse stereoselectivity, promising removal of the chiral auxiliary used, and wide variation of substrates. In the following paper, we report the sythesis of optically active talaromycins as an application of this method.

Acknowledgement. The authors are indebted to Takeda Science Foundation for financial support.

References and Notes

1. Iwata, C.; Hattori, K.; Uchida, S.; Imanishi, T. Tetrahedron Lett. 1984, 25, 2995. Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; Imanishi, T. Tetrahedron Lett. 1985, 26, 2221. Iwata, C.; Moritani, Y.; Sugiyama, K.; Fujita, M.; Imanishi, T. Tetrahedron Lett. in press.
2. Lynn, D.G.; Phillips, N.J.; Hutton, W.C.; Shabanowitz, J. J. Am. Chem. Soc. 1982, 104, 7319. Hutton, W.C., Phillips, N.J.; Graden, D.W.; Lynn, D.G. J. Chem. Soc., Chem. Commun. 1983, 864.
3. In dl series, some successful reports concerning such functionalization have appeared. cf. Schreiber, S.L.; Wang, Z. J. Am. Chem. Soc. 1985, 107, 5303. Schreiber, S.L.; Hulin, B. Tetrahedron Lett. 1986, 27, 4561.
4. The functionalization of enantiotopic groups has been achieved mainly by enzyme-catalyzed reactions but separation of enantiomers is very difficult. cf. Lam, L.K.P.; Hui, R.A.H.F.; Jones, J.B. J. Org. Chem. 1986, 51, 2047. Jones, J.B. Asymmetric Synthesis (ed. by Morrison, J.D.) 1985, 5, 309
5. Dekmezian, A.H.; Kaloustian, M.K. Syn. Commun. 1979, 9, 431.
6. Solladie, G. Synthesis 1981, 185.
7. Alkylations of α-sulfinyl ketones were known to proceeed very hardly. See, for example, Bartlett, P.A. J. Am. Chem. Soc. 1976, 98, 3305.
8. ^{1}H-NMR δ ($CDCl_3$). (7S)-**10a:** 1.63 (3H, s, C_1-Me), 2.56-2.62 (1H, m, C_8-H), 2.98 (1H, dd, J = 5, 11.5 Hz, C_7-H). (7R)-**10a:** 1.39-1.45 (1H, m, C_8-H), 1.66 (3H, s, C_1-Me), 3.36 (1H, dd, J = 5, 11 Hz, C_7-H).
9. Ratios of (3S)- and (3R)-**1** were estimated by a HPLC analysis (Shimazu LC-5A, Sumipac OA-2000A, 4mm x 250mm, n-hexane/i-propanol (28/2), UV-meter).
10. The ratio of (3S)- and (3R)-**1a** estimated by the HPLC analysis was found to be accord to the ratio obtained from isolated yields of the O-benzyl derivatives ((3S)- and (3R)-**11**).
11. Levenson, H.S.; Smith, H.A. J. Am. Chem. Soc. 1940, 62, 1556.

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