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α-ALLYLATED CHIRAL THIOXANONES: DIASTEREOSELECTIVE PREPARATION BY AN *S*-ALKYLATION/[2,3]-SIGMATROPIC REARRANGEMENT SEQUENCE.

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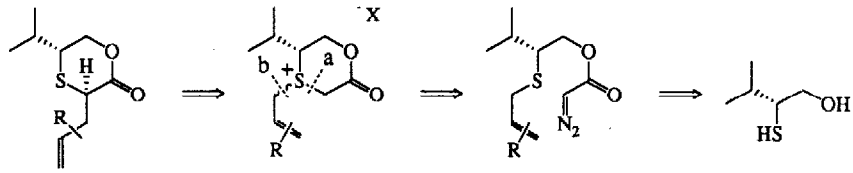
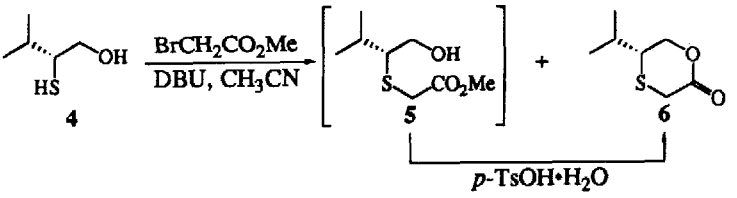
Abstract: *Diastereoselective S-allylation of thioxanone* ***6*** *and subsequent ylid formation/[2,3]-sigmatropic rearrangement delivers excellent Cα-induction. Non-stereospecific Cβ-induction results from scrambling of olefin geometry in the S-allylation step.*

We recently reported[2] thioxanone-based [2,3]-sigmatropic rearrangement methodology[3] for the preparation of Cα,Cβ-chiral thioxanones of general structure **1**. That chemistry, outlined below (**1** ⇒ **4**), delivers these α-alkylated thioxanones with excellent Cα,Cβ-induction starting from chiral auxiliary **4** by acid catalyzed cyclization of the key intermediate, α-diazoester **3**, to chiral thioxonium salt **2**. Subsequent sulfonium ylid formation with concomitant [2,3]-sigmatropic rearrangement delivered Cα,Cβ-chiral thioxanone **1**. Herein, we report an alternate strategy for the formation of chiral thioxonium salt **2** which proceeds by diastereoselective *S*-alkylation of a pre-formed thioxanone; i.e., bond **b** formation rather than bond **a** formation.

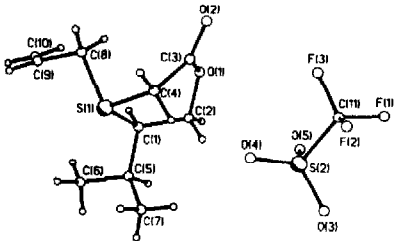


1 **2** **3** **4**

Unpleasant smelling β-hydroxythiol **4** ($[\alpha]_D$ +13.94°, *C* 1.55, $CHCl_3$) readily available in optically pure form from L-valine,[2] was *S*-alkylated with methyl bromoacetate (1.1 eq. DBU, dry CH_3CN, r.t.) to give hydroxyester **5** together with varying amounts of thioxanone **6**.[4] Complete lactonization was achieved by acidifying (0.5 eq. *p*-TsOH•H_2O) this reaction mixture and stirring at room temperature for 3 h giving **6** ($[\alpha]_D$ +137.6°, *C* 1.41, $CHCl_3$) in 64-75% overall yield from β-hydroxythiol **4**.

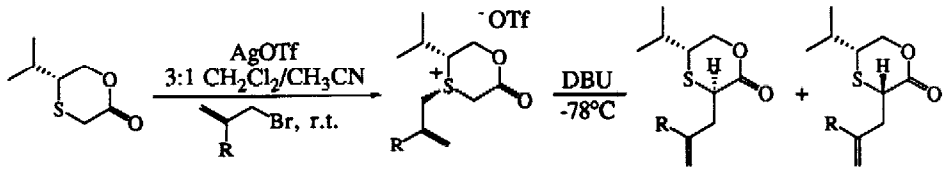


Surprisingly, attempts to *S*-allylate chiral thioxanone **6** using a variety of allylating agents and solvent conditions (for example: allyl bromide, CF_3CH_2OH, $CaCO_3$, r.t.;[5] allyl tosylate (neat), r.t. → 60°C; allyl mesylate, CH_3CN, r.t. → 60°C) failed, giving either recovered thioxanone or a complex mixture of decomposition products.[6] This led us to conclude that a more reactive allylating agent was required and to this end we turned to allyl trifluoromethanesulfonate (triflate).[7] While the Vedejs procedure[7] delivers allyl triflate, we found that its *in situ* preparation is much more convenient for the present application. Thus, dropwise addition of allyl bromide (10 eq.) to a methylene chloride/acetonitrile (3:1) solution of silver triflate (1.1 eq.) and thioxanone **6** (1.0 eq) at room temperature resulted in *S*-allylation to thioxonium triflate **7** in excellent crude yield. Recrystallization from EtOAc/Et_2O gave **7** in 44% yield and X-ray crystallographic analysis of this colorless thioxonium salt established that, as anticipated on the basis of steric considerations, *S*-allylation occurred on the thioxanone face opposite of the C6-isopropyl group. Not surprisingly, this six-membered ring heterocyle adopts a boat conformation.



X-Ray Structure of Thioxonium Triflate **7** (R=H).[8]

It is in fact not necessary to isolate these thioxonium triflates. Rather, dropwise addition of DBU (1.1 eq.) to the *S*-allylation reaction mixture completes a one-pot conversion of **6** to α-allylated **8** via the intermediary of a transient sulfonium ylid. As outlined in the next scheme, rearranged thioxanones **8** and **9** were obtained in 67-88% overall yield from **6** and the major product, *trans*-**8**,[9] was obtained in 96% diastereomeric excess. This is a kinetic product ratio since treating a 98:2 mixture of **8** and **9** (R=H) with DBU in a methylene chloride and acetonitrile (3:1) solution at room temperature resulted in equilibration, by enolization, to a 62:38 mixture. The **8/9** product ratio resulting from ylid formation/[2,3]-sigmatropic rearrangement is temperature independent over the range of room temperature to -78 °C (all giving 98:2 diastereoselectivity), but -78°C is preferred as it minimizes subsequent Cα equilibration. Moreover, direct Cα alkylation of **6** (1.0 eq. LDA, THF, -78°C; allyl bromide, HMPA, -78°C → -40°C; HOAc quench at -40°C) is essentially non-selective, giving **8** and **9** in 53% combined yield as a 59:41 mixture, respectively.

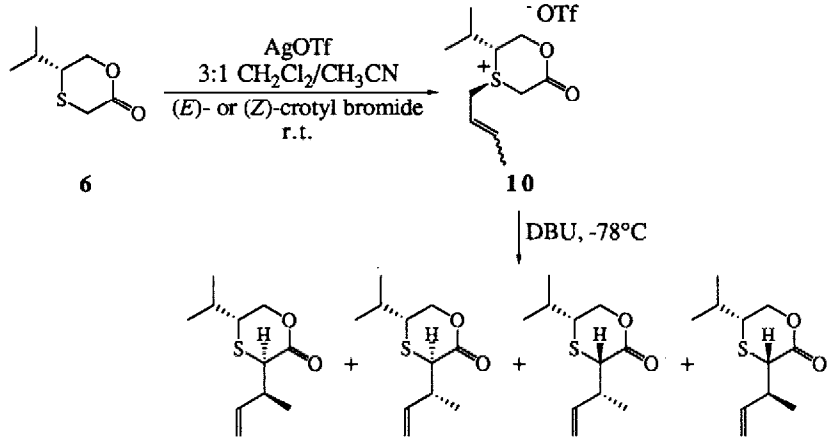


6 7 8 9

R =	% (8 + 9)	8 / 9 ratio[a]
H	88	98 / 2
CH_3	67	98 / 2
CH_2CH_3	72	98 / 2

[a]Ratio determined by capillary GLC.[10]

In light of these impressive results with 2-alkyl substituted allyl bromides, we were intrigued by the possibility of extending this methodology to crotyl bromides as it would deliver C_α, C_β-chiral thioxanone **1** (R=CH_3) via thioxonium salt 2 (R=CH_3). Indeed, *S*-crotylation of thioxanone **6** with (*E*)-crotyl bromide followed by ylid formation and rearrangement led to the anticipated thioxanone **11** as the major product, but with only 84% diastereoselectivity. Without attempting to optimize this reaction it was repeated using (*Z*)-crotyl bromide as the electrophile and we were surprised to find that again thioxanone **11**, not **12**, was the major product. These results indicate that silver triflate activation causes olefin isomerization so that both (*E*)- and (*Z*)-crotyl bromide give predominantly (*E*)-**10**. Attempts to effect S-crotylation under non-isomerizing condition were unsuccessful.



6 10 11 12 13 14

	% (11 - 14)	11 / 12 / 13 / 14 ratio[a]
(*E*)-crotyl bromide	63	84 / 6 / 6 / 4
(*Z*)-crotyl bromide	60	76 / 8 / 11 / 5

[a]Ratio determined by capillary GLC.[11]

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References and Notes:

1 (a) M.J.K. is a Sloan Fondation Fellow (1987-1991) and NIH RCDA recipient (1989-1994; ES00182). (b) Questions regarding X-ray crystallographic data should be addressed to M.M.O.

2 Kurth, M. L.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286.

3 For a review of chirality transfer via sigmatropic rearrangements, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B.

4 For the preparation of a related racemic thioxanone, see: Vedejs, E.; Gapinski, D. M.; Hagen, J. P. *J. Org. Chem.* **1981**, *46*, 5452.

5 Schmid, R.; Schmid, H. *Helv. Chim. Acta* **1977**, *60*, 1361.

6 (a) Vedejs *et al.* experienced similar difficulties in the *S*-alkylation of α-vinyltetrahydrothiophene with ethyl bromoacetate.[6b] (b) Vedejs, E.; Hagen, J. P.; Roach, B.L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185.

7 Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

8 Compound **7** (R = H) crystallizes from EtOAc/Et_2O in the orthorhombic space group, $P2_12_12_1$. The crystal data at 130 K are as follows: a = 7.874 (1) Å, b = 8.282 (1) Å, c = 23.357 (3) Å; ρ(calcd) = 1.53 g cm^{-3}; Z = 4; Syntex $P2_1$ diffractometer, MoKα radiation, λ = 0.71069 Å, graphite monochromator; 2θ(max) = 50°; 1451 reflections with $F > 4\sigma(F)$ and 91 parameters used in refinement; R = 0.055; crystallographic programs SHELXTL Rev. 5.1.

9 Stereochemical assignments were made by comparing ^{1}H NMR and capillary GLC data for **8** and **9** with those of our previously reported thioxanones:[2] **8** (R = H): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 [d, 3 H, J = 6.7 Hz, $C\underline{H}_3(CH_3)CH$], 1.04 [d, 3 H, J = 6.7 Hz, $CH_3(C\underline{H}_3)CH$], 1.88 [dtt, 1 H, J = 6.7, 6.7, 6.7 Hz, $C\underline{H}(CH_3)_2$], 2.35 (ddddd, 1 H, J = 1.0, 1.0, 7.5, 7.5, 15.0 Hz, $C\underline{H}HCH{=}CH_2$), 2.78 (ddddd, 1 H, J = 1.4, 1.4, 6.1, 6.1, 14.8 Hz, $CH\underline{H}CH{=}CH_2$), 3.29 (ddd, 1 H, J = 4.5, 6.4, 11.6 Hz, $C\underline{H}CH_2O$), 3.70 (dd, 1 H, J = 5.8, 7.6 Hz, CHC=O), 4.18 (dd, 1 H, J = 11.9, 11.9 Hz, $C\underline{H}HO$), 4.48 (dd, 1 H, J = 4.5, 12.0 Hz, $CH\underline{H}O$), 5.12 [dddd, 1 H, J = 1.0, 1.0, 1.0, 10.5 Hz, $CH{=}C\underline{H}H$ (*cis*)], 5.18 [dddd, 1 H, J = 1.5, 1.5, 1.5, 17.0 Hz, $CH{=}CH\underline{H}$ (*trans*)], 5.86 (dddd, 1 H, J = 6.4, 7.4, 10.1, 17.1 Hz, $C\underline{H}{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 18.88 [$\underline{C}H_3(CH_3)CH$],19.92 [$CH_3(\underline{C}H_3)CH$], 30.71 [$\underline{C}H(CH_3)_2$], 33.59 ($\underline{C}H_2CH{=}CH_2$), 36.11 ($\underline{C}HC{=}O$), 48.18 ($\underline{C}HCH_2O$), 68.61 ($CH_2O$), 117.65 ($CH{=}\underline{C}H_2$), 133.50 ($\underline{C}H{=}CH_2$), 170.73 (C=O); 1R (neat) 3081 (HC=), 2965, 2874, 1752 (C=O), 1644 (C=C), 1468, 1433, 1387, 1368, 1335, 1304, 1250, 1153, 1117, 1080, 1036, 995, 920 cm^{-1}. Anal. calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05; S, 16.01. Found: C, 59.87; H, 8.28; S, 15.88.

10 Capillary GLC analysis (initial temp. = 110°C; initial time = 2 min; heating rate = 2.0 °C/min; DB 1701 column; 30m x 0.259mm): R_t ($\mathbf{8}_{[R=H]}$) 13.4 min and R_t ($\mathbf{9}_{[R=H]}$) 12.0 min; R_t ($\mathbf{8}_{[R=Me]}$) 16.4 min and R_t ($\mathbf{9}_{[R=Me]}$) 15.2 min; R_t ($\mathbf{8}_{[R=Et]}$) 18.2 min and R_t ($\mathbf{9}_{[R=Et]}$) 17.1 min.

11 Capillary GLC analysis (initial temp. = 110°C; initial time = 2 min; heating rate = 2.0 °C/min; DB 1701 column; 30m x 0.259mm): R_t (**11**) 14.6 min, R_t (**12**) 14.5 min, R_t (**13**) 13.5 min, R_t (**14**) 13.3 min.

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