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STEREOSELECTIVE KETENE-CLAISEN REARRANGEMENT OF CHIRAL ALLYLTHIOETHERS

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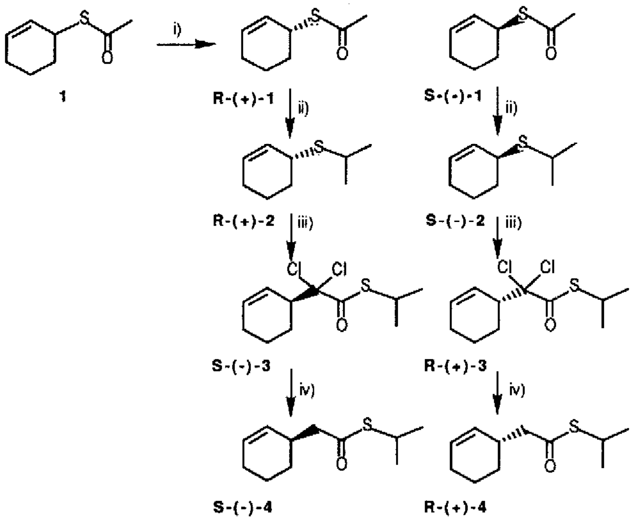
Abstract : ***A new method for the preparation of chiral β-branched, γ,δ-unsaturated thioesters and derivatives is presented, which involves the ketene-Claisen rearrangement of chiral allylthioethers. A novel synthesis of the starting chiral allylthioethers is also described.***

During our investigations of the ketene-Claisen rearrangement[1,2] with allylthioethers we became interested in examining the applicability of this unique intermolecular type of Claisen rearrangement in natural product synthesis and so studied its chemoselectivity and stereochemical course.

Though the Claisen rearrangement[3] predictably proceeds with high stereospecifity via a tightly ordered transition state, the reaction conditions are often too harsh for the survival of sensitive functional groups. In contrast, the rearrangement starting with allylthioethers presented here, can be run slightly above room-temperature. Allylthioethers proved to be superior to their oxygen analogues as far as yields and side-products were concerned[1,2,4,5]. Our results using chiral cyclic and open-chain allylthioethers are presented in Schemes I and II.

Initial attempts[4] to prepare optically pure cyclohexenylthioethers e.g. **2**, via optically pure cyclohexenols were not fully successful, since the asymmetric reduction[6] of cyclohexenone gave S-(-)-cyclohexen-3-ol in an ee of only 66%. Therefore, we took the more classical approach of enantiomer separation (Scheme I). Cyclohexene-thiolacetates[7] 1 could easily be separated into their pure enantiomers by chromatography on triacetyl cellulose[8] on a 10-20 gram scale. Subsequent deacetylation and alkylation of the resulting thiols yielded the desired chiral thioethers **2**. No racemization took place during the basic deacetylation step, as detected by the R-(-)-TFAE-shift method[9] (2,2,2-triflouro-1-(-9-anthryl)-ethanol).

Both enantiomers **2** were rearranged under the standard conditions[1]. The optical activity of the thioesters **3** thus formed, was again determined by R-(-)-TFAE-shift experiments. These revealed that a practically complete chirality-transfer occurred in the cyclic allylthioethers **2**: **R-(+)-1** of 89% ee gave **S-(-)-3** of 88% ee, whereas **S-(-)-1** of 96.4% ee yielded **R-(+)-3** of 95.4% ee. The absolute stereochemistry of **1** - **4** has been proven by comparison of the TFAE-shifted ^{1}H-NMR spectra and the optical rotation with **S-(-)-2** obtained[4] from known S-(-)-cyclohexene-3-ol[6]. Both halocompounds **3** were easily reduced[1] to **4**. No loss of optical purity was observed during this dechlorination as was checked by the TFAE-shift method.

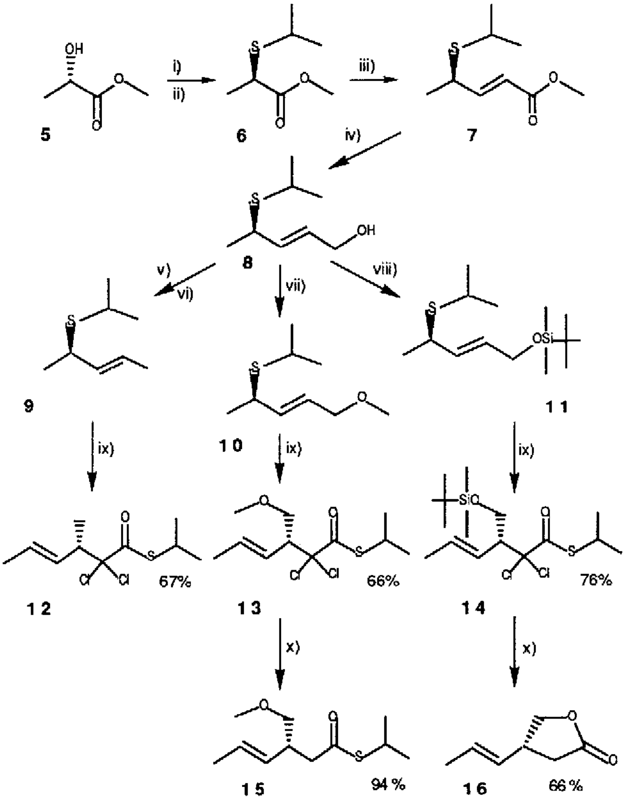


Scheme I[18]: i) triacetyl cellulose, EtOH; ii) 1) 5%-NaOH, 59 - 96%; 2) EtOH, EtONa, ^{i}PrBr, 53 - 69%; iii) Zn/Cu, CCl_3COCl, reflux, Et_2O, 4 h, 60 - 83%; iv) AcOH, Zn, 100° C, 2 - 3 h, 86 - 92%.

We were now interested to tackle the open-chain problem (Scheme II). Starting from commercially available S-(-)-methyl-lactate **5** (ee ca. 98%) we prepared the thioderivative **6** via thiolate-substitution of the tosylate of **5**. This tosylate proved to be highly prone to racemization[10]. Reproducible optical rotations, $[\alpha]_D = -36.6° - -37.5°$ ($c = 1.5$, $CHCl_3$), could be obtained when the reaction mixtures were carefully quenched with water below +5° C and traces of base were excluded during vacuum distillation. The thiolether **6** could only be synthesized under controlled mild conditions to avoid partial racemization[11]. Eu(hfc)$_3$-shift experiments[12] indicated an unchanged ee of 98%. Ester **6** was reduced to its corresponding alcohol, whose Mosher ester[13] revealed in a ^{1}H-NMR measurement a diastereomeric ratio of 98.2/1.8 and thus verified the LSR-experiment of **6**.

As expected the crucial step towards compounds **9** - **11** proved to be the unprecedented chain elongation of ester **6** via the corresponding aldehyde and its in situ Wittig olefination. This one-pot procedure in analogy to Krief's communication[14] provided the α,β-unsaturated E-ester **7** in 76% yield. The optical purity of this material was again checked by two different NMR methods. Shift experiments of **7** with R-(-)-TFAE showed an ee of 84 - 90%. The NMR spectrum of the Mosher ester of the corresponding alcohol **8** revealed an ee of 84%. This alcohol, which was accessible from **7** by DIBAH reduction in 95% yield, was transformed into the olefin **9** by LAH reduction of the corresponding allylic bromide[15]. This liquid allylic halide had to be used quickly after preparation because it tended to decompose rapidly to an intractable syrup. Compound **10** and **11** were easily available in 89% and 99%, respectively, by methylation and silylation of alcohol **8**. Only compound **10** showed a shift with R-(-)-TFAE. The ^{1}H-NMR spectrum revealed an ee of 84.8% (vide supra).

Allylic thioether **9** served as a model to scrutinize the stereochemical course of the ketene-Claisen rearrangement with dichloroketene in open-chain systems. Compounds **10** and **11** were chosen to check the chemoselectivity of this reaction. Under the standard conditions[1] the rearranged thioester **12** was obtained in 67% yield after distillation. By using the previous R-(-)-TFAE shift technique one could distinguish the signals of C-3 methyl groups of both enantiomers. The ee was determined as 80.6%. Thus, the rearrangement exhibited a chirality-transfer of at least 95%. Compounds **10** and **11** could also be rearranged by this procedure in 66% and 76% yield respectively. Exclusive sulfur migration was observed by the ^{1}H-NMR spectra of the crude products. R-(-)-TFAE shift experiments revealed an ee of 82.8% for **13** and 83% for **14**. Again this means a chirality-transfer of at least 98%[16]. Thioester **13** was dechlorinated[1] without any loss of optical purity to ester **15** in 94% yield. During an analogous dechlorination of **14** the as yet unknown lactone **16** was spontaneously formed in 66% yield.



Scheme II[18]: i) TosCl, pyr, 0°C, 6.5 h, 69%; ii) K_2CO_3, ^{i}PrSH, CH_3CN, 0° C to r.t., 5 d, 91%; iii) 1) DIBAH, CH_2Cl_2, -78° C, 90 min; 2) $Ph_3PCHCOOCH_3$, -78° C to r.t., 12 h, 76% E-isomer; iv) DIBAH, THF, 0° C, 50 min, 95%; v) Ph_3P, CBr_4, CH_3CN, r.t., 81%; vi) LAH, THF, 3 h, reflux, 56%; vii) NaH, THF, reflux, CH_3I, 89%; viii) imidazole, ^{t}BuMe$_2$SiCl, DMF, 16 h, 99%; ix) Zn/Cu, Et_2O, reflux, 3 - 4 h, CCl_3COCl; x) Zn, AcOH, 100° C, 2 - 3h.

This intermolecular variant of the well known Claisen rearrangement is characterized by its experimental simplicity and virtually complete chirality-transfer from a C-S to a C-C bond. Interestingly, if in the same molecule both allylic sulphur and allylic oxygen can compete for dichloroketene, complete chemoselection in favour of the more nucleophilic sulphur is observed. Thus, both **10** and **11** yielded only the thioesters **13** and **14**, respectively. Amide analogues[17] of the dehalogenated compound **12** were recently used as building blocks for assembling pine sawflies pheromones. Further investigations, especially with sugar derivatives, are in progress.

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18) $[\alpha]_D^{20}$-values ($CHCl_3$): **R-(+)-1**: +261.8° (c 0.5); **S-(-)-1**: -267.0° (c 0.5); **R-(+)-2**: +212.5° (c 0.9); **S-(-)-2**: -215.7° (c 0.7); **R-(+)-3**: +5.8° (c 0.5); **S-(-)-3**: -3.7° (c 0.5); **R-(+)-4**: +38.9° (c 1.0); **S-(-)-4**: -38.1° (c 0.8); **6**: +131.5° (c 1.0); **7**: +108.0° (c 0.2); **8**: +42.6° (c 0.7); **9**: +19.6° (c 0.7); **10**: +34.4° (c 0.8); **11**: +33.2° (c 0.8); **12**: -25.6° (c 0.8); **13**: -16.9° (c 0.6); **14**: -4.3° (c 0.6); **15**: -26.7° (c 0.7); **16**: -3.2° (c 0.8).

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