# Diastereoselective Thia-Claisen Rearrangement of Pyrrolidinone-Derived Ketene *N*,*S*-Acetals

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Dedicated to Professor Sir Jack Baldwin FRS, an inspirational scientist, on his 70th birthday

**Abstract:** Thia-Claisen rearrangements of *S*-allylic ketene *N*,*S*-acetals were carried out using substrates with an external allylic stereogenic centre. High levels of diastereoselectivity were observed only when a bromine substituent was introduced onto the double bond.

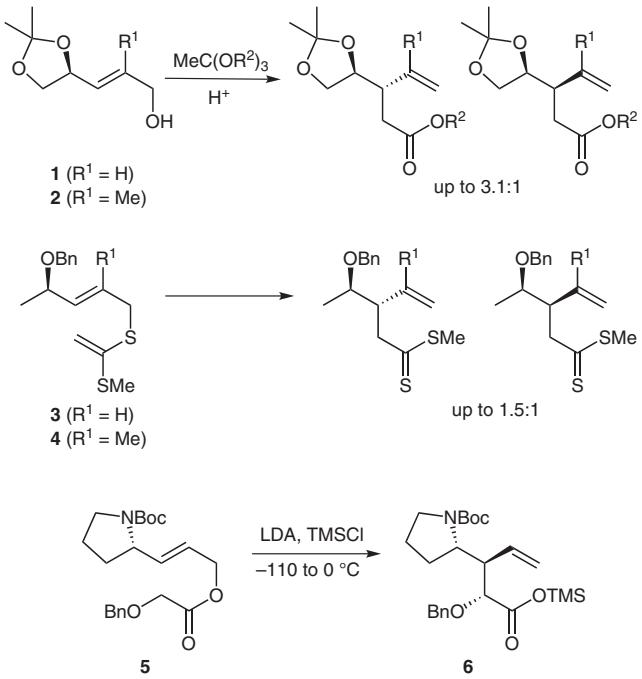
**Key words:** sulfur, bromine, diastereoselectivity, pericyclic reactions, rearrangements

The Claisen rearrangement of allyl enol ethers and its variants have been extensively studied and widely used in synthesis.[1] Among the desirable features of these reactions is the reliable and predictable stereochemistry of the products, arising through a chair-like transition state.

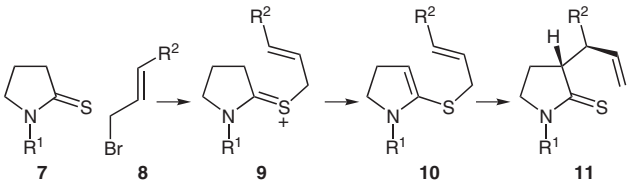
As a consequence of this ordered transition state, 1,3-chirality transfer from a stereogenic centre within the six-atom chain of the [3,3]-sigmatropic process is generally excellent. Asymmetric induction from external stereogenic centres has been much less frequently reported.[2] In particular there are very few cases in which a stereogenic centre attached to the 'allyl fragment' has been shown to be effective in inducing asymmetry. For example, Johnson–Claisen rearrangement of either the *E*- or *Z*-isomers of alcohols **1** and **2** gives the corresponding products in a ratio of no greater than 3.1:1 (Scheme 1).[3] Similar results are obtained with a tetrahydropyranyl ether[4] or a sugar-derived 1,3-dioxane[5] in place of the acetonide moiety, although in the latter case, use of the *Z*-alkene geometry raises the diastereoselectivity to >10:1. Slightly better results are obtained in the Ireland–Claisen rearrangement of esters derived from **1**; diastereomeric ratios up to 4.4:1 are obtained from the *E*-isomer, and up to 9:1 from the *Z*-isomer.[6] The thia-Claisen rearrangements of compounds **3** (*E*-isomer) and **4** (*E*- and *Z*-isomers) also proceed with low levels of stereoselectivity (Scheme 1).[7]

A rare example of efficient asymmetric induction in such reactions comes in the Ireland–Claisen rearrangement of pyrrolidine substrate **5**; in this case, product **6** is obtained as a single stereoisomer (Scheme 1).[8,9]

One variant of the Claisen rearrangement which has received relatively little attention is the thia-Claisen rearrangement of *N*,*S*-ketene acetals. Alkylation of thioamides or thiolactams such as **7** with allylic halides **8** and deprotonation of the resulting salts **9** gives *N*,*S*-ketene acetals **10** (Scheme 2). Rearrangement occurs spontaneously to give **11**, and proceeds with high levels of diastereoselectivity.[10]




**Scheme 1**




**Scheme 2** Thia-Claisen rearrangement of *N*,*S*-ketene acetals

As part of an ongoing project to synthesise the core of the sarain alkaloids,[10c] we were interested in using such a rearrangement to prepare compound **11** ($R^1$ = Bn, $R^2$ = $CH_2OH$) in enantiomerically pure form. In this letter, we describe our achievement of this goal through the use of allylic bromides bearing a sacrificial stereogenic centre which can subsequently be excised.

The initial substrate selected was allylic bromide **14a**. Conversion of 1,2:5,6-di-*O*-isopropylidene-D-mannitol

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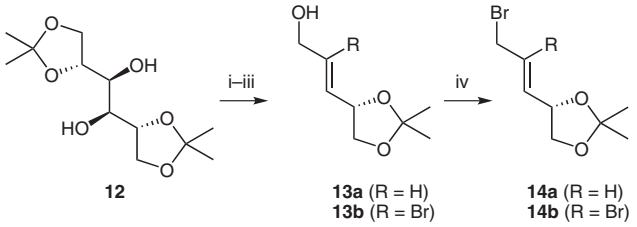
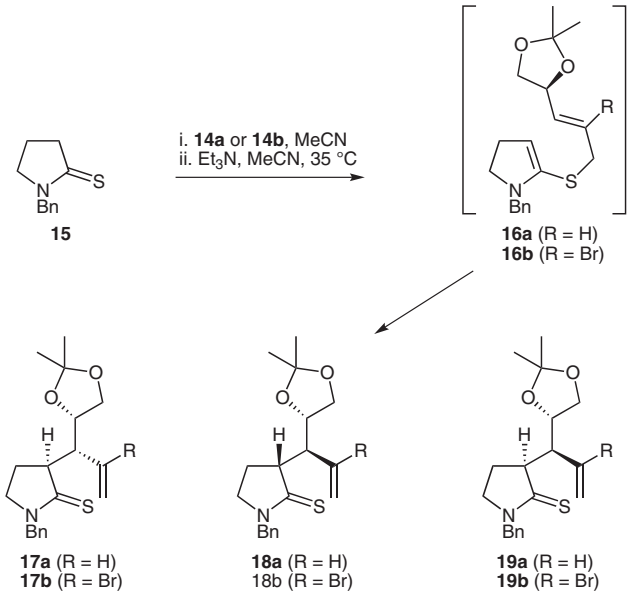



**Scheme 3** *Reagents and conditions:* (i) $NaIO_4$, $NaHCO_3$, $H_2O$, 0 °C to r.t.; (ii) $EtO_2CCHRPO(OEt)_2$, $K_2CO_3$, $H_2O$, 0 °C to r.t.; (iii) DIBAL-H, $CH_2Cl_2$, –78 °C, **13a** (75%) from **12**; **13b** (43%) from **12**; (iv) NBS, $PPh_3$, $CH_2Cl_2$, 0 °C to r.t., **14a** (93%); **14b** (67%).




**Scheme 4** Thia-Claisen rearrangements

(**12**) into allylic alcohol **13a** was achieved using the procedure of Marshall et al.,[11] which consists of periodate cleavage, Wadsworth–Emmons reaction under aqueous conditions, and DIBAL-H reduction. Treatment of the alcohol **13a** with *N*-bromosuccinimide and triphenylphosphine led to allylic bromide **14a** (Scheme 3).[12]

Alkylation of *N*-benzylpyrrolidine-2-thione (**15**) with bromide **14a** was followed by deprotonation with triethylamine in acetonitrile to give the transient intermediate **16a**; following thia-Claisen rearrangement, this afforded a mixture of thiolactams **17a**, **18a** and **19a**, three of the four possible stereoisomeric products (Scheme 4) (see below for stereochemical assignment). The results are summarised in Table 1 (entry 1).

The major products were the expected isomers **17a** and **18a**, arising from a chair transition state, with only a small amount of a third diastereomer **19a**. However, the levels of diastereoselectivity were disappointingly low (2.5:1), reflecting a low level of facial selectivity imparted upon the exocyclic double bond by the adjacent stereocentre in **16a**. We postulated that this lack of selectivity could be due to the presence of more than one significantly populated rotamer about the bond between the alkene and the stereogenic centre.

**Table 1** Product Ratios in Thia-Claisen Rearrangements

| Entry | Bromide | Ratio **17**:**18**:**19**[a] | Yield of **17** (%)[b] | Yield of **18** (%)[b] | Yield of **19** (%)[b] |
|---|---|---|---|---|---|
| 1 | **14a** | 2.5:1:0.1 | 38 | 10 | 1 |
| 2 | **14b** | 1:12.2:0.6[c] | 2 | 52 | 2 |

[a] Ratios measured from the $^1H$ NMR spectrum of the crude reaction mixture.
[b] Isolated yields of single diastereomers.
[c] A trace amount of another compound, thought to be the fourth diastereomer, was also observed.

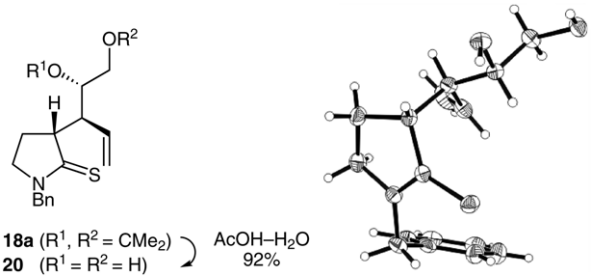
In an attempt to bias the conformation of **16** towards a single rotamer, an analogue of **14a** was chosen in which the alkene bears a further substituent; this should induce significant $A^{1,3}$-strain, restricting rotation about the relevant C–C bond, and improving the diastereoselectivity of the sigmatropic rearrangement.[13]

The chemistry used previously was thus modified by the use of a brominated phosphonate reagent, $EtO_2CCH(Br)PO(OEt)_2$,[14] in the Wadsworth–Emmons step to give the corresponding ester as a 1.6:1 *Z*:*E* mixture (Scheme 3). After reduction to the alcohol **13b**, the geometric isomers were separated and the *Z*-isomer converted into allylic bromide **14b**.

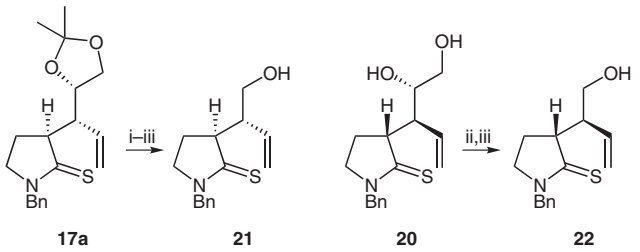
This allylic bromide was next employed in the thia-Claisen rearrangement (Scheme 4) and, pleasingly, afforded the products **17b**–**19b** with good diastereoselectivity (Table 1, entry 2).[15] The major product in this rearrangement was the (2*R*,3′*S*,4′*S*)-isomer **18b**, in contrast to the nonbrominated substrate which afforded primarily the (2*S*,3′*R*,4′*S*)-isomer **17a**.

Assignment of the configuration of products **17**–**19** was accomplished through a combination of crystallography and chemical correlations.

Removal of the acetonide from **18a** with 60% aqueous acetic acid afforded the crystalline diol **20**, whose structure was unambiguously assigned by X-ray crystallography (Scheme 5).[16]




**Scheme 5** Preparation of diol **20** and thermal ellipsoid plot; ellipsoids are drawn at 50% probability level and the H atoms have an arbitrary radius




**Scheme 6** *Reagents and conditions*: (i) 60% aq AcOH, 88%; (ii) $NaIO_4$, $SiO_2$, $CH_2Cl_2$, $H_2O$; (iii) $NaBH_4$, EtOH, THF, **21** (51%), **22** (31%) (two steps).

Assignment of the stereochemistry of **17a** was achieved by cleavage of the protected diol unit. Deprotection of **17a** with aqueous acetic acid (as for **18a**), followed by cleavage with silica-supported periodate[17] and reduction with sodium borohydride gave alcohol **21**, whereas oxidative cleavage and reduction of diol **20** gave alcohol **22** (Scheme 6). These products had identical $^1$H NMR spectra but opposite specific rotations.[18] As the stereochemistry of **22** could be deduced from the previously obtained crystal structure of **18a**, **21** could be identified as its enantiomer and hence **17a** assigned the structure shown.

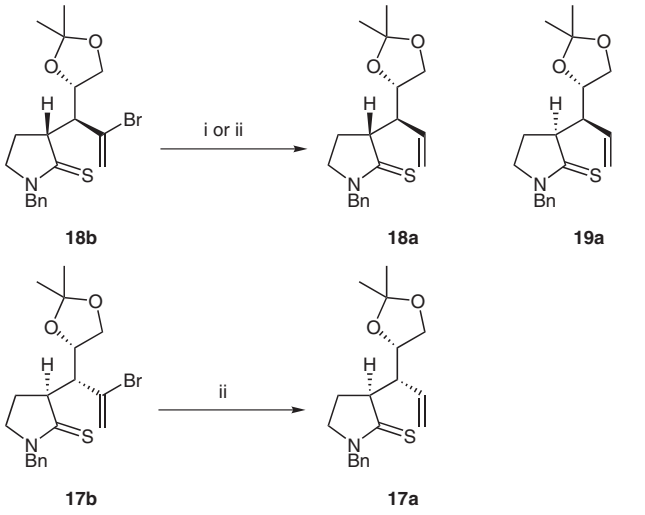
Correlation between the brominated and nonbrominated series of compounds was next sought by carrying out palladium-catalysed debromination of the major bromoalkene product **18b**. Initially, triethylammonium formate was used as the reducing agent;[19] however, this gave a mixture of two nonbrominated products, **18a** and **19a**, due to epimerisation either preceding or following the debromination event (Scheme 7). While this result did not allow assignment of the stereostructure of **18b**, it did indicate that **18a** and **19a** were epimeric at the position α to the thiocarbonyl group.

Epimerisation was avoided through the use of tributyltin hydride as the reductant[20] in the palladium-catalysed debromination. Under these conditions, **18a** was obtained as a single isomer, confirming that **18b** had the structure shown and indirectly confirming the structure of **19a**.

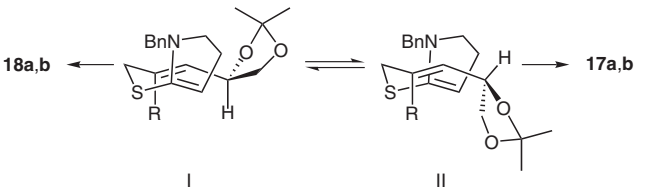
Debromination of bromoalkene **17b** under the same conditions gave solely **17a**, establishing the stereochemical equivalence of these two compounds.

Definitive assignments of five of the six rearrangement products could thus be made; minor bromoalkene product **19b** was not obtained in sufficient quantity to carry out its debromination, and its stereostructure was assigned only tentatively, by analogy with **19a**.

The stereochemical course of the thia-Claisen reaction can be rationalised by considering the reactive conformations of intermediates **16a** and **16b**. If it is assumed that (i) the reaction takes place through a chair transition state, and that (ii) reaction of the 'nucleophilic' *N*,*S*-ketene acetal fragment on the 'electrophilic' allyl sulfide fragment occurs *anti* to the allylic oxygen substituent, then two possible reactive conformations can be drawn, these are depicted as **I** and **II** in Scheme 8. Conformation **I** gives rise to products **18a** and **18b** while conformation **II** leads to products **17a** and **17b**.




**Scheme 7** *Reagents and conditions*: (i) $Et_3N$, HCOOH, $Pd(OAc)_2$, $PPh_3$, DMF, 65 °C, **18a** (35%) + **19a** (21%); (ii) $Bu_3SnH$, $Pd(PPh_3)_4$, THF, reflux, **18a** (50%) from **18b**; **17a** (60%) from **17b**.




**Scheme 8** Proposed reactive conformations of **16a** (R = H) and **16b** (R = Br)

The preference for reaction on the allylic sulfide component to take place *anti* to the oxygen substituent can be understood if the reaction is considered as a nucleophilic attack on this component; the newly forming σ-bond is then stabilised by overlap with the low-lying σ* orbital of the C–O bond.[21] Such an effect, in related Ireland–Claisen rearrangements, has been characterised computationally by Kahn and Hehre as involving the more electron-poor face of the electrophilic component.[22]

In the case of brominated intermediate **16b**, $A^{1,3}$-strain ensures that conformation **I** is strongly favoured over **II**, and the major product is **18b**. For the nonbrominated analogue **16a**, the absence of a double bond substituent means that the energy difference between the two possible transition states is much smaller and indeed a slight preference for product **17a**, arising through conformation **II**, is observed.[23]

It is noteworthy that in previously reported examples of asymmetric induction in Claisen-type rearrangements, the presence of a methyl substituent on the double bond had little effect on diastereoselectivity (e.g. **1** vs. **2**, **3** vs. **4**, Scheme 1). By contrast, in the present example the introduction of a bromine substituent greatly increases the

magnitude of the diastereoselectivity, and reverses its sense. Furthermore, the bromine substituent can be removed after the rearrangement step.

In conclusion, we have ensured high levels of diastereoselectivity in the thia-Claisen rearrangement of chiral substrates through the judicious exploitation of allylic strain. Further studies into these reactions, and their application in synthesis, are ongoing.

## Acknowledgment

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(15) A mixture of thioamide **15** (116 mg, 0.61 mmol), bromide **14b** (200 mg, 0.67 mmol), MeCN (1 mL) and 4 Å molecular sieves (250 mg) was stirred under an argon atmosphere for 4 d. Further MeCN (2 mL) was added and the mixture warmed to 35 °C. $Et_3N$ (94 μL, 0.67 mmol) was added and the resulting solution was stirred at 35 °C for 7 h. The mixture was cooled to r.t., diluted with $CH_2Cl_2$ (30 mL) and washed with 2% citric acid (2 × 50 mL). The combined aqueous washings were extracted with $CH_2Cl_2$ (50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the crude product (190 mg, 76%). Flash chromatography ($SiO_2$; EtOAc–PE, 1:19) afforded **18b** (130 mg, 52%) as a pale yellow oil; $R_f$ 0.43 (EtOAc–PE, 15:85); $[\alpha]_D^{20}$ +31.5 (*c* = 1.08, $CHCl_3$). IR ($CHCl_3$ cast): 2983, 2934, 2874 (CH), 1625 (C=C), 1499, 1452, 1316 (C=S) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.28 (3 H, s) and 1.34 [3 H, s, $C(CH_3)_2$], 2.30–2.40 (2 H, m, $NCH_2CH_2$), 3.21 (1 H, br t, *J* = 8.5 Hz, CHC=S), 3.51 (1 H, ddd, *J* = 11.0, 8.5, 7.0 Hz) and 3.62 (1 H, ddd, *J* = 11.0, 8.8, 5.2 Hz, $NCH_2CH_2$), 3.76 (1 H, dd, *J* = 8.5, 6.8 Hz, CHHO), 3.88 [1 H, dd, *J* = 10.1, 1.8 Hz, $H_2C$=C(Br)CH], 4.10 (1 H, dd, *J* = 8.5, 6.1 Hz, CHHO), 4.44 (1 H, ddd, *J* = 10.1, 6.8, 6.1 Hz, CHO), 4.79 (1 H, d, *J* = 14.6 Hz) and 5.16 (1 H, d, *J* = 14.6 Hz, $PhCH_2$), 5.51 (1 H, dd, *J* = 1.8, 0.5 Hz) and 5.90 (1 H, dd, *J* = 1.8, 0.4 Hz, $C=CH_2$), 7.26–7.32 (5 H, m, ArH). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 22.2 ($NCH_2CH_2$), 26.0 and 26.5 [$C(CH_3)_2$], 51.9 ($PhCH_2$), 52.8 ($NCH_2CH_2$), 55.2 [$H_2C$=C(Br)CH], 56.9 (CHC=S), 68.7 ($CH_2O$), 74.7 (CHO), 110.1 [$C(CH_3)_2$], 119.8 (C=$CH_2$), 127.9, 128.2 and 128.7 (aromatic CH), 133.5 (C=$CH_2$), 135.3 (aromatic C), 203 (C=S). MS ($CI^+$, $CH_4$): *m*/*z* = 410 (16), 412 (14) [$MH^+$], 352 (46), 354 (50) [$MH^+ - Me_2CO$], 338 (63), 330 (100) [$MH^+$ – HBr]. HRMS: *m*/*z* [$MH^+$] calcd for $C_{19}H_{25}{}^{79}BrNO_2S$: 410.0789; found: 410.0799.
(16) **X-ray data**: $C_{16}H_{21}NO_2S$, *M* = 291.40; *T* = 150(2) K; orthorhombic, $P2_12_12_1$, *a* = 8.6108(10), *b* = 13.2760(16), *c* = 13.3204(16) Å; *Z* = 4; $D_c$ = 1.271 g/cm$^3$; *F*(000) = 624; μ(Mo–$K_\alpha$) = 0.214 $mm^{-1}$; 12892 reflection, 3586 independent ($R_{int}$ = 0.0336) measured on a Bruker SMART APEX CCD diffractometer using Mo–$K_\alpha$ radiation; *R*1 = 0.0350, *wR*2 = 0.0834 (3346 reflections $F^2 > 2\sigma F^2$), *R*1 = 0.0382, *wR*2 = 0.0855 (all data). Atomic coordinates and further crystallographic details have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 687669. Copies of these data can be obtained by applying to CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.; fax: +44 (1223)336033; email: deposit@ccdc.cam.ac.uk.
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(18) Data for **21**: $R_f$ 0.23 (EtOAc–PE, 30:70); $[\alpha]_D^{20}$ –73.2 (*c* = 0.40, $CHCl_3$). IR ($CHCl_3$ cast): 3399 (br, OH), 2923, 2875 (CH), 1635 (C=C), 1508, 1453, 1310 (C=S) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.87 (1 H, ddt, *J* = 12.8, 8.8, 6.1 Hz) and 2.17 (1 H, dtd, *J* = 12.8, 9.1, 5.9 Hz, $NCH_2CH_2$), 2.62 (1 H, br s, OH), 3.02 (1 H, m, $H_2C$=CHCH), 3.33 (1 H, ddd, *J* = 9.1, 6.3, 3.6 Hz, CHC=S), 3.44 (1 H, ddd, *J* = 11.2, 9.1, 6.1 Hz) and 3.49 (1 H, ddd, *J* = 11.2, 8.8, 5.9 Hz, $NCH_2CH_2$), 3.71 (1 H, dd, *J* = 11.5, 6.5 Hz) and 3.84 (1 H, dd, *J* = 11.5, 9.1 Hz, $CH_2OH$), 4.90 (1 H, d, *J* = 14.3 Hz) and 5.05 (1 H, d, *J* = 14.3 Hz, $PhCH_2$), 5.10 (1 H, dd, *J* = 10.5, 1.8 Hz) and 5.20 (1 H, dd, *J* = 17.3, 1.8 Hz, CH=$CH_2$), 5.64 (1 H, ddd, *J* = 17.3, 10.5, 8.8 Hz, CH=$CH_2$), 7.28–7.34 (5 H, m, ArH). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 23.1 ($NCH_2CH_2$), 49.3 ($H_2C$=CHCH), 51.8 ($PhCH_2$), 52.8 ($NCH_2CH_2$), 55.1 (CHC=S), 63.0 ($CH_2OH$), 118.4 (CH=$CH_2$), 128.1, 128.3 and 128.8 (aromatic CH), 134.9 (aromatic C), 135.6 (CH=$CH_2$), 202.7 (C=S). MS ($CI^+$, $CH_4$): *m*/*z* = 290 (22) [$M + C_2H_5$]$^+$, 262 (100) [$MH^+$], 244 (32) [$MH^+ - H_2O$], 191 (25). HRMS: *m*/*z* [$M + H^+$] calcd for $C_{15}H_{20}NOS$: 262.1266; found: 262.1260.
For **22**: $[\alpha]_D^{20}$ +71.4 (*c* = 0.28, $CHCl_3$).
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