Highly Stereoselective Synthesis of a Chiral Methyl Group by a Facially Controlled Sigmatropic [1,5]-Hydrogen Shift

Christoph Dehnhardt,[†] Matthew McDonald,[‡] Sungsook Lee,[‡] Heinz G. Floss,[‡] and Johann Mulzer*,[†]

Institut für Organische Chemie, Universität Wien
Währinger Strasse 38, Vienna, Austria
Department of Chemistry, Box 351700
University of Washington
Seattle, Washington 98195-1700

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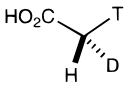
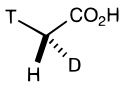
Chiral methyl groups in the form of chiral acetic acid (*R*)- and (*S*)-**1** have been invaluable for the elucidation of numerous biochemical mechanisms.[1] So far, two basically different approaches to (*R*)- and (*S*)-**1** have been reported: The first one (Arigoni strategy)[2] uses a cascade of ene−retroene reactions to introduce the three isotopes of hydrogen at one and the same carbon atom via a mechanistically defined stereochemical pathway. Optical activity is achieved by chemical optical resolution of a suitable alcohol intermediate. The second one (Cornforth,[3] Floss,[4] Altman[5] strategy) hinges on S_N2 reactions of anionic hydrogen donors with configurationally defined epoxides or primary tosylates. In this case, asymmetry is introduced by optical resolution (Cornforth), by means of a chiral reagent (Floss) or by starting from the chiral carbon pool (Altman). Recently, we reported a synthesis of (*R*)- and (*S*)-**1** via a base-induced [1,3]-hydrogen shift,[6] but with a disappointingly low ee-value of ca. 40%.



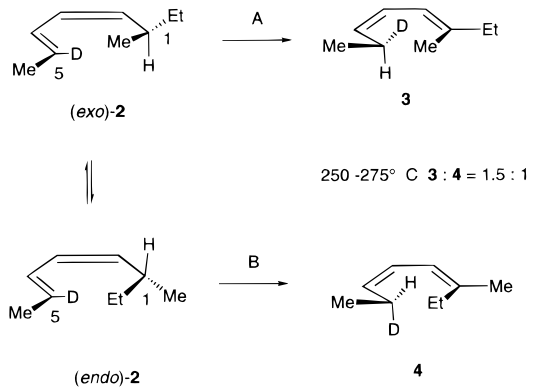
(*S*)-**1**



(*R*)-**1**

In this communication we want to disclose a novel synthesis of (*S*)-**1** in high optical purity that is based on the mechanism-controlled chirality transfer involved in thermal sigmatropic [1,5]-hydrogen shifts. In contrast to [1,2]-, [2,3]-, and [3,3]-sigmatropic rearrangements which belong to the standard repertoire of organic synthesis, [1,5]-migrations, despite intensive mechanistic investigations in the early seventies,[7,8] have found only limited application in stereoselective transformations. This is mainly due to the formation of side products, and the reversibility of the reaction and the lack of absolute stereocontrol, for which Roth's reaction[8] (Scheme 1) may serve as an illustration. According to the Woodward−Hoffmann rules[9] the [1,5]-hydrogen migration proceeds suprafacially with respect to the cisoid butadiene skeleton.

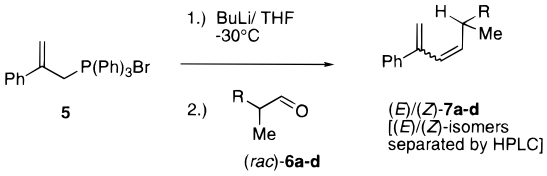
Scheme 1



(*exo*)-**2**

(*endo*)-**2**

Scheme 2



Two reactive diene conformers *exo*- and *endo*-**2** are involved, from which dienes **3** and **4** are generated in a 1.5:1 ratio at 250 °C along pathways A and B, respectively. These dienes are (*E*/*Z*) isomers and contain the stereogenic center at C-5 in *opposite configurations*. Thus, although the Woodward−Hoffmann rules are obeyed by conformers *exo*- and *endo*-**2** individually, the overall rearrangement lacks stereocontrol. Even more seriously, about 27% of the starting material **2** is still present after 2 h at 250 °C. Attempting to drive the rearrangement to completion at 275 °C, Roth discovered that altogether ten products are formed and the [1,5]-hydrogen shift obviously becomes a mess.

On considering how Roth's experiment might be adapted to the synthesis of (*S*)-**1** it occurred to us that dienes (*Z*)-**7a**−**d** might be suitable candidates for the following reasons. First of all, the isomerization of **7** to **8** should be irreversible as two trisubstituted olefinic bonds are generated from a mono- and a disubstituted one. Additionally, due to the presence of the 2-phenyl substituent, the π system changes from a cross-conjugated one in **7** to a more stable linearly conjugated one in **8**. Earlier experiments[10] have also shown that the phenyl group stabilizes **7** and **8** toward polymerization and thermodimerization and prevents further double bond migrations in **8**.

Increasing the bulkiness of substituent R should result in a clear preference of pathway A over B, but it remained to be tested whether the required selectivity of >100:1 could be achieved in this way. At this stage, the configurational purity of the 1,2-double bond in the rearrangement product, which was easy to check via analytical GC, could serve as an analytical probe of the cleanness of the concomitant [1,5] chirality transfer. Hence, dienes **7a**−**d** were prepared as (*E*/*Z*) isomer mixtures from phosphonium bromide[11] **5** and racemic aldehydes *rac*-**6a**−**d** as shown in Scheme 2 and separated by HPLC. Isomers (*Z*)-**7a**−**d** were submitted to thermal rearrangements at 200 °C in benzene. In fact, the reaction was complete within 4 h and a maximum of two products were found. (*E*)- and (*Z*)-**8a**−**c** were formed from (*Z*)-**7a**−**c** and (*E*)-**8d** was the sole product from the rearrangement of (*Z*)-**7d**, as

[†] Universität Wien.
[‡] University of Washington.

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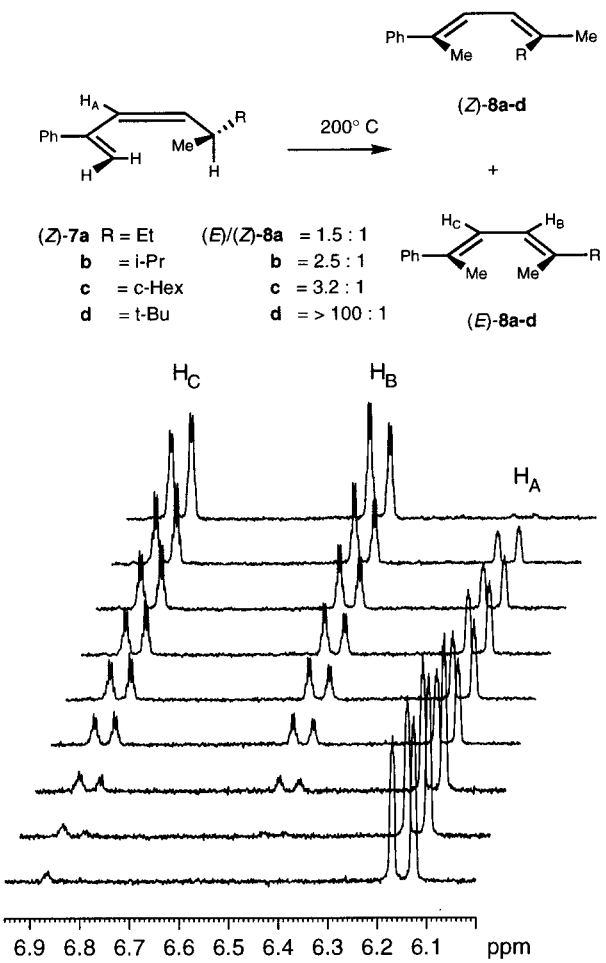


Figure 1. The thermolysis was observed by ^{1}H NMR. The spectra in Figure 1 show the proton signals which identify the product (*E*)-**8d** of the rearrangement.

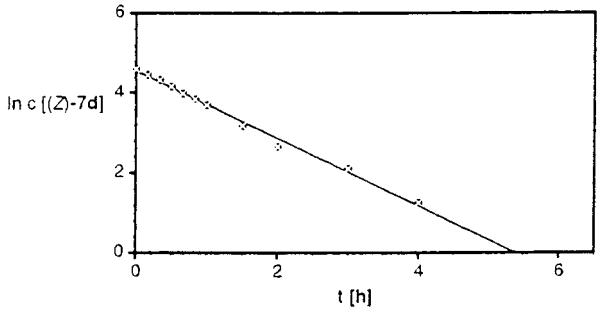
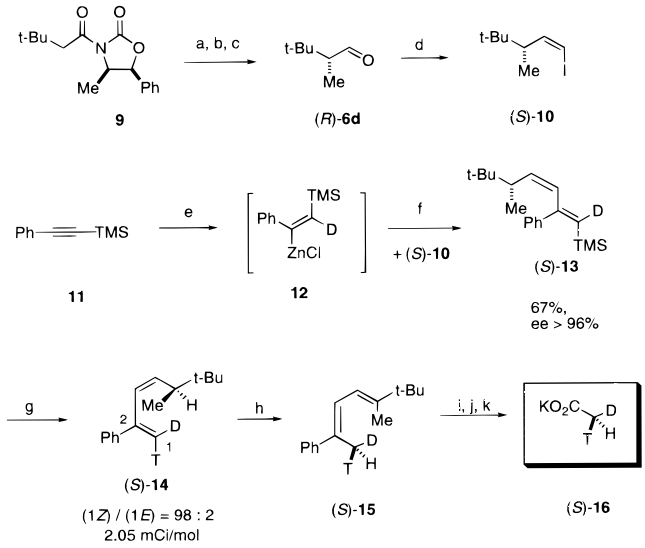


Figure 2. The figure shows the first-order rate law of the thermolysis (for example, diene (*Z*)-**7d**).

shown by ^{1}H NMR (Figure 1). All rearrangements strictly followed a first order rate law and were completely irreversible (Figure 2).

This result encouraged us to use nonracemic deuterium−tritium labeled (*S*)-**14** for the synthesis of acetic acid (*S*)-**1**. The stereocontrolled preparation of our model diene (Scheme 3) is centered around a Negishi-coupling of the chiral vinyl iodide (*S*)-**10** with the vinyl zinc derivative **12**, obtained from trimethylsilylphenyl acetylene[12] **11** via deuteriomagnesiation-transmetalation.[13] Specifically, aldehyde (*R*)-**6d** was prepared from the Evans oxazolidinone **9** by routine operations[14] and converted to (*S*)-**10** via a (*Z*)-selective Wittig olefination.[15] Acetylene **11** was

Scheme 3[a]



[a] Conditions: (a) NaHMDS, THF, −78 °C, 2 h then MeI (77%); (b) BnSH, BnSLi, THF, 0 °C, then 1 M LAH; (c) PCC, DCM; (d) NaHMDS, THF, −78 °C, $Ph_3PCH_2I_2$, (65%); (e) 2D-iBuMgBr, Cp_2TiCl_2, then 1 M $ZnCl_2$ in THF; (f) $Pd(PPh_3)_4$ (67%); (g) CF_3CO_2T in pentane, 5 °C, 20 min (94%); (h) 4 h at 200 °C in benzene (95%); (i) O_3, PPh_3, DCM, −78 °C; (j) TFAA, UHP, DCM, 2 h, reflux; (k) 1 N KOH, 15 min (36%, 3 steps, 2.05 mCi/mol, spec. act., >95:5 e.r.).

treated with [2-$^2H_1$]-isobutylmagnesium bromide/Cp_2TiCl_2 and then with $ZnCl_2$ to generate **12** which was added in situ to (*S*)-**10** under palladium catalysis.[16] Diene (*S*)-**13** was obtained as a single isomer and submitted to tritiodesilylation, which proceeded with retention of configuration to furnish the desired diene (*S*)-**14**.

Thermal rearrangement as described led quantitatively to (*S*)-**15**, which was converted into the potassium salt (*S*)-**16** (specific radioactivity 2.05 mCi/mol) via an ozonolysis/Baeyer−Villiger oxidation sequence. The enzymatic analysis[17] of (*S*)-**16** established an ee value of >90% (limits of accuracy).[18]

In conclusion a new and efficient synthesis of chiral acetic acid (*S*)-**1** (9 steps from **9** with 11% overall yield) has been developed based on a diastereofacially controlled [1,5]-hydrogen shift. Within the limits of analysis the chirality transfer from **14** to **15** appears to be quantitative. In addition, the synthesis provides information on the stereoselectivity of other important reactions, namely the tritiodesilylation of 1,3-dienylsilanes and the deuteriomagnesiation−Negishi coupling of alkynes and vinyl iodides. The oxidative degradation of **15** to **16** proceeds without any loss of optical purity. The extension of the method to dienes derived from the chiral carbon pool (such as dienes synthesized from lactaldehyde and glyceraldehyde) and kinetic studies of the reaction will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all compounds described (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) In several analyses the sample gave *F* values[17] indistinguishable within the error limits from those of an authentic,[4] optically pure sample of (*S*)-[$^2H_1$,^{3}H]acetate analyzed simultaneously.