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Enantioselective Construction of Spiro{cyclopropane-1,4'-bicyclo[3.3.0]oct-1-en-3-ones}[1]

Andreas Stolle,[a,b] Heike Becker,[a] Jacques Salaün,[b]* Armin de Meijere[a]*

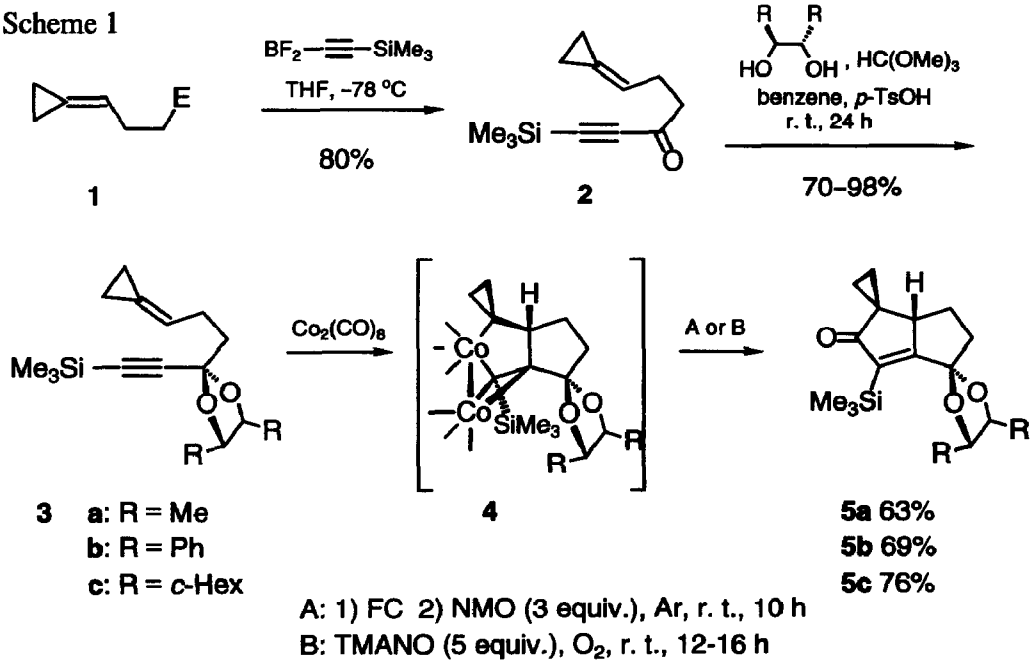
Institut für Organische Chemie, Georg-August-Universität Göttingen,[a] Tammannstraße 2, D-37077 Göttingen, Germany
Laboratoire des Carbocycles, Institut de Chimie Moléculaire d'Orsay,[b] Université de Paris-Sud, F-91405 Orsay, France

Keywords: Pauson-Khand reaction, intramolecular; methylenecyclopropanes, double bond activation in; spiro{cyclopropane-1,4'-bicyclo[3.3.0]oct-1-en-3-ones}; enantiomerically pure compounds; stereoselection.

Abstract: Intramolecular Pauson-Khand reactions of 1,6-enynes **3a-c** with a methylenecyclopropane terminator and a chiral acetal moiety adjacent to the triple bond gave spiro{cyclopropane-1,4'-bicyclo[3.3.0]oct-1-en-3-ones} **5a-c** in good yields with a diastereoselectivity of up to 6.4:1. The major diastereomer of **5b** was converted to enantiomerically pure bicyclo[3.3.0]octane-3,8-dione **8**, which showed a negative peak at 287 nm in the CD curve, consistent with an assumed (*5R*) configuration.

Intramolecular Pauson-Khand reactions (PKR)[2] of 1,6-enynes[3] to form bicyclo[3.3.0]oct-1-en-3-ones proceed particularly well when the double bond is part of a methylenecyclopropane moiety.[4] In order to demonstrate the full potential of this approach to spiro{cyclopropane-1,4'-bicyclo[3.3.0]oct-1-en-3-ones} we have tested the possibility of asymmetrically inducing the cyclization with a chiral auxiliary adjacent to the triple bond in the 1,6-enyne, especially since only a few examples of PKR with asymmetric induction have been reported to date.[5]

Scheme 1



1 2

3 **a**: R = Me
b: R = Ph
c: R = *c*-Hex

4

5a 63%
5b 69%
5c 76%

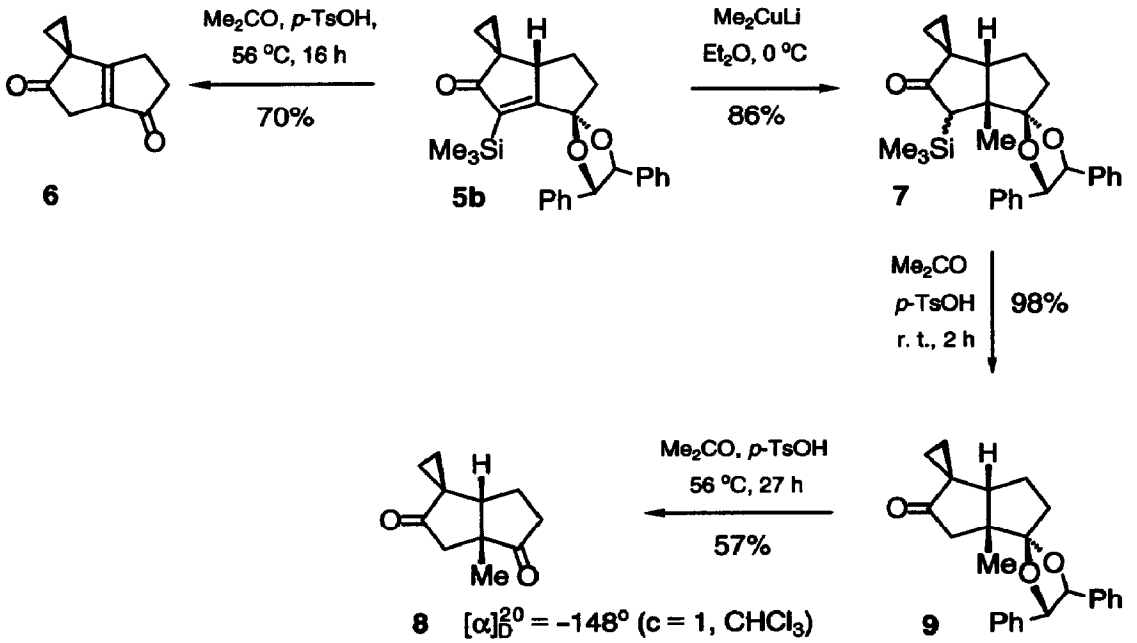
A: 1) FC 2) NMO (3 equiv.), Ar, r. t., 10 h
B: TMANO (5 equiv.), O_2, r. t., 12-16 h

As Magnus et al. have demonstrated,[3] high diastereoselectivities can be obtained in the intramolecular PKR. On the basis of their mechanistic rationalization it was conceived that a cyclopropylidenealkyne of type **3** with a C_2-symmetric acetal moiety next to the triple bond – by favouring an intermediate with the configuration as in **4** – might lead to an asymmetric induction in the cyclization step.[6] The 6-cyclopropylidene-1-hexyn-3-one **2** was prepared by reacting the ester **1**[7] with lithium trimethylsilylacetylide in the presence of boron trifluoride etherate[8] (80% yield), and converted to the acetals **3a-c** by transacetalization[9] with the appropriate ethanediol[10] and trimethyl orthoformate (Scheme 1).

Although heavily substituted, the trimethylsilyl protected alkynes **3a-c**[12] underwent trialkylamine oxide promoted PKR[13] quite well (63–76% yield). The diastereoselection in the cyclization of **3a** with a dimethylsubstituted acetal moiety was only 2 : 1, according to GC, but increased to 5 : 1 for the diphenyl **3b** and even 6.4 : 1 for the dicyclohexyl derivative **3c**.[11]

The diastereomers of **5b** and **5c** could be separated by column chromatography.[14] Further transformations were performed with the major diastereomer of **5b**, which was assumed to have (5*R*) configuration on the basis of the adopted mechanism with a preferred intermediate **4**.[15] In order to determine the absolute configuration of the bicyclo[3.3.0]octenone skeleton, it was attempted to cleave off the chiral auxiliary in the acetal moiety. Upon treatment of **5b** with acetone and *p*-toluenesulfonic acid, however, not only acetal

Scheme 2



cleavage, but also double bond migration occurred to yield the achiral bicyclo[3.3.0]octenedione **6** (Scheme 2). Therefore, lithium dimethylcuprate was first added to the enone moiety in **5b**, before the dioxolane was hydrolyzed. Surprisingly, acetal cleavage in the resulting **7** (2-*endo*/2-*exo* = 1 : 7) was quite slow, within 2 h at room temperature only protiodesilylation occurred to give **9**. Only upon prolonged heating under reflux, **9**

eventually gave the dione **8** with $[\alpha]_D^{20} = -148\ ^\circ$ (c = 1, $CHCl_3$). The CD curve with a negative peak at 287 nm (ellipticity of 550°) is consistent with the absolute configuration[16] being (5*R*) as assumed on the basis of the preferred orientation of bulky groups in the intermediate **4**.

This model study demonstrates a new asymmetric variant of the intramolecular Pauson-Khand reaction. It is conceivable that further tailoring of the acetal moiety may lead to even higher diastereoselectivities. To achieve this, it is however essential to have the methylenecyclopropyl terminator in the precursor enyne; control experiments showed that enynes without this end group reacted only poorly and only under more drastic conditions (hexane, 110 °C), albeit with nearly the same diastereoselectivity.

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14. All new compounds (except **3a**, **3b**, **5a**, **6**, and the minor diastereomers of **5b,c**) were fully characterized by spectroscopic techniques (^{1}H NMR, ^{13}C NMR, IR, MS) and their molecular formulas established by elemental analysis and/or HRMS. Physical data for relevant compounds: **2**: IR (neat) 3030, 2970, 2930, 2160 (C≡C), 1680 (C=O), 1255, 1115, 855, 770 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.32 (s, 9 H), 0.98–1.06 (m, 4 H), 2.49–2.59 (m, 2 H), 2.68–2.77 (m, 2 H), 5.72–5.82 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –0.83, 1.96, 2.05, 26.15, 44.59, 97.70, 101.91, 115.67, 122.57 – **3a**: IR (neat) 2940, 2900, 2830, 1420, 1365, 1240, 1190, 1070, 855, 830, 750 cm^{-1}; ^{1}H NMR (250 MHz, C_6D_6) δ 0.14 (s, 9 H), 0.82–0.95 (m, 4 H), 1.02 (d, 3 H), 1.18 (d, 3 H), 2.32–2.41 (m, 2 H), 2.86–2.90 (m, 2 H), 3.47 (dq, 1 H), 4.08 (dq, 1 H), 5.57–5.84 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –0.23, 1.99, 16.44, 17.84, 26.22, 39.55, 79.22, 79.43, 80.08, 101.82, 104.61, 117.23, 121.30. – **3b**: IR (KBr) 3052, 2960, 2903, 1253, 1216, 1194, 1122, 1095, 1060, 1041, 1026, 976, 951, 843, 768, 701, 533

cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 9 H), 0.95–0.96 (m, 4 H), 2.14–2.21 (m, 2 H), 2.45–2.54 (m, 2 H), 4.58 (d, 1 H), 4.99 (d, 1 H), 5.75–5.81 (m, 1 H), 7.12–7.29 (m, 10 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –0.24, 2.03, 26.13, 39.40, 86.20, 86.51, 89.55, 103.55, 104.24, 117.14, 121.58, 126.72, 127.12, 128.15, 128.34, 128.45, 135.70, 137.59. – **3c**: IR (neat) 3050, 2925, 2853, 2166 (C≡C), 1450, 1250, 863, 843 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.14 (s, 9 H), 0.85 (s, 4 H), 1.00–2.08 (m, 21 H), 2.30–2.43 (m, 3 H), 2.26–2.38 (m, 2 H), 3.54–3.63 (m, 1 H), 4.01–4.09 (m, 1 H), 5.88–5.96 (m, 1 H); ^{13}C NMR (62.9 MHz, C_6D_6) δ –0.17, 2.11, 2.27, 26.43, 26.70, 26.90, 27.00, 28.12, 29.64, 30.21, 30.58, 40.62, 41.58, 41.74, 84.29, 84.55, 87.72, 102.46, 107.11, 117.91, 121.49. – **5a**: IR (neat) 2980, 2880, 1680 (C=O), 1600, 1235, 1110, 1070, 840; ^1H NMR (250 MHz, C_6D_6) δ 0.48–0.46 (m, 1 H), 0.51, 0.52 (s, 9 H), 0.57–0.70 (m, 1 H), 0.90–1.12 (m, 7 H), 1.30–1.54 (m, 2 H), 1.86–2.12 (m, 7 H), 2.30–2.36 (m, 1 H), 3.42–3.56 (m, 1 H), 3.60–3.75 (m, 1 H); ^{13}C NMR (62.9 MHz, C_6D_6) δ 0.21, 0.33, 14.41, 14.50, 14.61, 15.64, 16.59, 18.72, 25.21, 25.61, 33.46, 33.83, 40.86, 40.89, 78.20, 78.64, 79.00, 79.52, 110.49, 111.15, 138.55, 139.00, 188.67, 189.00, 211.42. – **5b** IR (KBr) 2937, 1695 (C=O), 1121, 845, 699, 668 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.60 (s, 9 H), 0.55–0.66 (m, 2 H), 0.71–0.79 (m, 2 H), 1.41–1.54 (m, 2 H), 2.10–2.22 (m, 1 H), 2.32–2.42 (m, 1 H), 3.08 (dd, 1 H), 4.92 (d, 1 H), 5.21 (d, 1 H), 7.10–7.27 (m, 8 H), 7.37–7.42 (m, 2 H); ^{13}C NMR (62.9 MHz, C_6D_6) δ 0.45, 14.43, 15.05, 24.65, 34.14, 39.93, 50.12, 84.85, 86.27, 113.34, 126.68, 127.29, 128.49, 128.87, 136.41, 137.85, 138.15, 187.15, 211.48; $[\alpha]_D^{rt}$ = 218.1°; minor diastereomer: ^1H NMR (250 MHz, C_6D_6) δ 0.63 (s, 9 H), 0.64–0.77 (m, 2 H), 1.01–1.08 (m, 1 H), 1.14–1.22 (m, 1 H), 1.36–1.55 (m, 2 H), 2.21–2.27 (m, 2 H), 2.87 (dd, 1 H), 5.07 (d, 1 H), 5.27 (d, 1 H), 7.11–7.45 (m, 1 H). – ^{13}C NMR (62.9 MHz, C_6D_6) δ 0.27, 14.43, 14.9025.69, 33.39, 41.55, 52.85, 83.91, 85.07, 111.67, 135.72, 138.88, 140.36, 187.70, 211.47. – **5c**: IR (neat) 2927, 2852, 1694 (C=O), 1244, 1123, 844 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.54 (s, 9 H), 0.49–0.68 (m, 2 H), 0.84–2.05 (m, 28 H), 2.96 (dd, 1 H), 3.64 (dd, 1 H), 3.76 (dd 1 H); ^{13}C NMR (62.9 MHz, C_6D_6) δ 0.52, 14.22, 14.92, 24.56, 26.26, 26.34, 26.53, 26.71, 28.54, 29.28, 30.24, 30.82, 34.09, 39.70, 40.84, 42.31, 49.51, 82.89, 83.74, 111.65, 136.62, 188.68, 211.52; minor diastereomer:^1H NMR (250 MHz, C_6D_6) δ 0.51 (s, 9 H), 0.48–2.30 (m, 30 H), 2.71 (dd, 1 H), 3.52 (dd, 1 H), 3.79 (dd, 1 H).

15. The relative configuration of compounds **5a-c** at C-5 could not be established by 2D-NMR (NOESY) spectroscopy.

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