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A CONVENIENT ROUTE TO 5-METHYL-3,7-OCTADIENIC ACID FROM 2,4-HEXADIENAL VIA UMPOLUNG AND DOUBLE COPE REARRANGEMENT 1)

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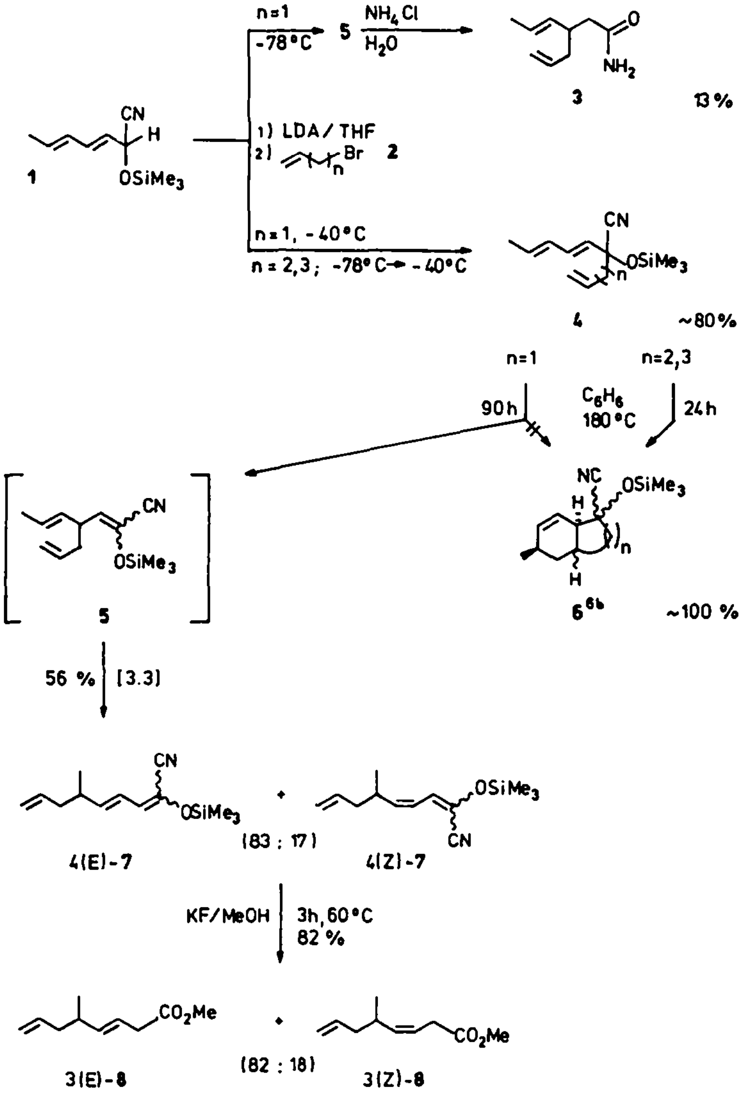
Abstract: The addition product of 2,4-hexadienal and trimethylsilyl cyanide **1** reacts after deprotonation with allylic bromide **2** (n=1) to the triene **4** (n=1) which on heating undergoes double Cope rearrangement forming α-trimethylsiloxy nitriles 4(E)-**7** and 4(Z)-**7**. These compounds are smoothly transformed into 3(E)- and 3(Z)-5-methyl-3,7-octanoic acid methyl esters 3(E)-**8** and 3(Z)-**8**. The reaction sequence may be synthetically useful since it is supposed to be applicable to different substituent patterns.

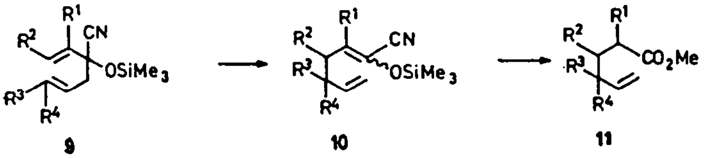
Trimethylsilyl cyanide has been shown to add regioselectively to carbonyl groups of α,ß-unsaturated aldehydes 3) employing as catalysts zinc iodide 3,4), aluminium chloride 3f,5), and cyanide ions 3c,3f,4) or, as we recently found 6), the very efficient tetrabutylammonium iodide. From these adducts LDA produces ambident anions, which react with a variety of alkylating agents mainly or exclusively in α-position 3b,6b). Since the group for umpolung can be removed under extremely mild conditions the whole reaction sequence has been developed into a valuable method for the synthesis of α,ß-unsaturated ketones via umpolung 3b,6a).

We have already shown that this procedure can easily be extended to 2,4-dienals. Adduct **1**, obtained in 95% yield from 2,4-hexadienal and trimethylsilyl cyanide, 3b) is smoothly deprotonated by LDA at -78°C. Thereby an ambident anion is formed, which principally can be alkylated at the α,γ or ε-position. Again very high α-regiospecificity is observed: with methyl iodide 3b), isopropyl iodide 3b) and, as demonstrated recently, unsaturated bromides **2** (n=2,3) 6b), where 95% of α-adducts are observed with no evidence for the γ- or ε-adducts in the crude reaction product (^{1}H NMR). With allyl bromide **2** (n=1) the same result can be achieved to yield **4** (n=1) if the alkylation is performed at -40°C from the very beginning and not started at -78°C as with the other examples cited. Only **2** (n=1) reacts with the anion of **1** already at -78°C forming thereby a α/γ -product mixture **4** (n=1) : **5** = 62 : 38 from which in addition to **4** (n=1) amide **3** can be isolated in 13% yield by treatment of the crude product with aqueous ammonium chloride (cf. 6a)). Probably solvent separated ion pairs are responsible for this substantial γ-attack of **2** (n=1) at -78°C. With increasing reaction temperature contact ion pairs become more important 7) and the observed higher selectivity would therefore be expected due to the directing effect of the properly situated gegenion 8).

Recently, we have reported on the smooth intramolecular Diels-Alder reactions of **4** (n=2,3) at 180°C where the cycloaddition to **6** (n=2,3) occurs in nearly quantitative yield 6b). Herewith we describe that with product **4** (n=1), however, no [4+2] cycloaddition product **6** (n=1) is formed. Instead, nitriles 4(E)-**7** and 4(Z)-**7** were isolated in reasonable yields, which have not been optimized. Methanolysis of these nitriles produces methyl 5-methyl-3(E),7-octadienoate 3(E)-**8** and its 3(Z)-isomer 3(Z)-**8** in 82% yield without affecting the E/Z ratio. Apparently the transformation **4**→**7** involves two consecutive Cope rearrangements passing through intermediate **5** which, however, could not be detected throughout the rearrangements (^{1}H NMR). Obviously, the first [3.3] rearrangement (formation of the acrylonitrile derivative **5**, cf. 9)) has a smaller driving force than that of the dienic nitrile **7**.



Adopting our method of umpolung, F.E. Ziegler et al. have already synthesized dienes **9**. These were transformed by a single Cope rearrangement to **10**. Subsequent solvolysis 9) affords **11** in good yields. On this basis the same group has developed a versatile method for constructing steroidal sceletons 10).



The transformation **4** (n=1)→ **7** therefore appears as a logical extension of the sequence **9**→**10**. Judging on our experience with umpolung of α,ß-unsaturated aldehydes 3b,6b), and on Ziegler's results on the corresponding Cope rearrangement 9,10), additional substituents should be tolerated both in the dienic and allylic moiety of **4** without blocking the two consecutive Cope rearrangements. Starting with appropriate dienals and allylic halides a great variety of substituted 3,7-octadienoates should be accessible.

We are grateful to the Fonds der Chemischen Industrie and the BASF Aktiengesellschaft, Ludwigshafen, for support of this study.

EXPERIMENTAL PART

2-(2-Propenyl)-2-trimethylsiloxy-3(E),5(E)-heptadiene nitrile (**4**; n=1): Addition of 3.919g(20.0 mmol) **1** in 8 ml THF to 22 mmol LDA in 20 ml THF at 78 °C produced a yellow precipitate. After adjusting the temperature to -40 °C 2.66 g (22.0 mmol) allyl bromide (**2**; n=1) was added during 15 min. After stirring the red orange solution for 12 h at -40 °C, 20 ml saturated NH_4Cl solution was added at room temperature. The aqueous layer was extracted with 3x10 ml petrol ether. After drying the organic phases over $MgSO_4$ and evaporating the solvents, the crude product 4.00 g (85%) yielded 3.55 g (75%) (**4**; n=1), b.p. 45 °C/$2\cdot10^{-2}$ Torr (Kugelrohr).

IR (film) (cm^{-1}): 3080, 3020, 1635, 1655. ^1H nmr (400 MHz, $CDCl_3$): δ =0.14 (s, 9H, $OSiMe_3$), 1.76 (dd, 7-H), 2.47 (mc, 1'-H_a), 2.57 (mc, 1'-H_b), 5.17 (ddt, 3'-H_a), 5.18 (ddt, 3'-H_b), 5.47 (d, 3-H), 5.75 (ddt, 2'-H), 6.02 (mc, 5-H), 6.45 (dd, 4-H); J (Hz): $J_{3.5}$=0.6, $J_{5.7}$=1.5, $J_{3'a.3'b}$=1.7, $J_{6.7}$=6.6, $J_{2'.1'a/b'}$= 7.2, $J_{4.5}$=10.4, $J_{3'b.2'}$=10.5, $J_{1'a.1'b}$=13.7, $J_{3.6}$=15.2, $J_{3.4}$=15.5, $J_{3'a.2'}$=16.8 -
$C_{13}H_{21}$ NOSi (235.3) Calc.: C, 66.33; H, 8.99; N, 5.95. Found: C, 66.34; H, 9.09; N, 5.88.

Stereoisomers of 6-methyl-2-trimethylsiloxy-2,4(E),8-nonatriene nitrile (4(E)-**7**) and 6-methyl-2-trimethylsiloxy-2,4(Z),8-nonatriene nitrile (4(Z)-**7**): 1.18 g (5.01 mmol) (**3**; n=1) in 5 ml benzene were heated in a sealed tube at 180 °C for 90 h (monitored by an ^1H nmr experiment with 96 mg (0.42 mmol) (**4**; n=1) in 0.4 ml C_6D_6). From both samples the solvent was evaporated and the residue (1.22 g) distilled: 720 mg (56%) b.p. 75-85 °C/$5\cdot10^{-1}$ Torr (Kugelrohr) of 83 % 4(E)-**7** (consisting of 2(Z),4(E)-**7** and 2(E),4(E)-**7** 69:31) and 17% 4-(Z)-**7** (consisting of 2(E),4(Z)-**7** and 2(Z),4(Z)-**7** 59:41 or 41:59). The amount of isomers was calculated from the intensities of the 6-CH_3 ^1H nmr signals.

IR (film) (cm^{-1}): 3070, 2210, 1595, 1635. ^1H nmr (400 MHz, $CDCl_3$): 2(Z),4(E)-**7** (δ): 0.26 (s, 9H, $OSiMe_3$), 0.99 (s, 3H, 6-Me), 5.71 (ddt, 8-H), 5.82 (ddd, 5-H), 5.99 (dd, 3-H), 6.26 (ddd, 4-H); J (Hz): $J_{3.5}$=0.8, $J_{4.6}$=1.2, $J_{6\text{-}Me.6}$=6.8, $J_{7.8}$=7.0, $J_{5.6}$=7.7, $J_{3.4}$=10.8, $J_{8.9b}$=11.0, $J_{4.5}$=15.6, $J_{8.9a}$=16.4. - 2(E),4(E)-**7** (δ): 0.23 (s, 9H, $OSiMe_3$), 1.00 (s, 3H, 6-Me), 5.72 (ddt, 8-H), 5.80 (dd, 5-H), 8.18-6.36 (m, 3-H, 4-H); J (Hz): $J_{6\text{-}Me.6}$=6.8, $J_{7.8}$=7.0, $J_{5.6}$=7.5, $J_{8.9b}$=11.0, $J_{4.5}$=14.3, $J_{8.9a}$=16.4 -2(E),4(Z)-**7** (δ): 0.26 (s, $OSiMe_3$), 0.97 (s, 6-Me), $J_{6\text{-}Me.6}$=6.8 Hz. - 2(Z),4(Z)-**7** (δ): 0.24 (s, 9H, $OSiMe_3$), 0.96 (s, 3H, 6-Me). $J_{6\text{-}Me.6}$=6.8 Hz. - Common signals of all isomers (δ): 1.98-2.16 (m, 7-H), 2.27-2.37 (m, 6-H), 4.95-5.03 (m, 2H, 9-H_a, 9-H_b). -
$C_{13}H_{21}NOSi$ (235.4) Calc.: C, 66.33; H, 8.99; N, 5.95. Found: C, 66.10, H, 8.92; N, 5.73.

Methyl 5-methyl-3(E),7-octadienoate (3(E)-**8** and methyl 5-methyl-3(Z),7-octadienoate (3(Z)-**8**): 240 mg (1.02 mmol) **7** were heated under reflux with 60 mg KF in 5 ml dry methanol. After evaporation the residue was dissolved in hexane, washed with saturated NH_4Cl, dried over $MgSO_4$, concentrated and distilled. From the residue 170 mg (99%) were distilled 140 mg (82%) **8**, b.p. 75-80 °C/4 Torr (Kugelrohr), containing 82% 3(E)-**8** and 18% 3(Z)-**8** (from 5-Me and -CO_2Me ^1H nmr signals).

IR (film) (cm^{-1}): 3060, 1635, 1735. ^1H nmr (400 MHz, $CDCl_3$). 3(E)-**8** (δ): 0.95 (d, 3H, 5-Me), 1.97 ($\underline{A}$B, 6-H_a), 2.05 (A$\underline{B}$, 6-H_b), 5.19 (mc, 5-H), 2.98 (mc, 2-H), 3.62 (s, 3H, CO_2Me), 4.93 (ddt, 8-H_b), 4.95 (ddt, 8-H_a), 5.42 ($\underline{A}$B, 4-H), 5.45 (A$\underline{B}$, 3-H), 5.70 (ddt, 7-H); J (Hz): $J_{6.8b}$= 1.1, $J_{6.8a}$=1.5, $J_{8.8a}$=2.1, $J_{4.5}$=2.9, $J_{2.3}$=5.4, $J_{5.6b}$=6.8, $J_{6b.7}$=6.8, $J_{5.5\text{-}Me}$=6.8, $J_{5.6a}$=7.1, $J_{6a.7}$=7.1, $J_{7.8b}$=10.5, $J_{6.6a}$= 13.9, $J_{3.4}$=15.3, $J_{7.8a}$=16.8, - 3(Z)-**8** (δ): 0.93 (d, 3H, 5-Me), 3.63 (s, 3H, -CO_2Me), 4.90-4.98 (m, 2H, 8-$H_{a/b}$), 5.69 (ddt, 7-H); J (Hz): $J_{5.Me\text{-}5}$=6.8, $J_{7.6}$=7.2, $J_{7.8b}$=10.2, $J_{7.8a}$=17.1
$C_{10}H_{16}O_2$ (168.2) Calc.: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.56.

2-(2-Propenyl)-3(E)-pentene carboxamide (**3**) and nitrile **4** (n=1): Addition of 1.95 g (10.0 mmol) **1** in 4 ml THF to 11.0 mmol LDA in 10 ml THF at -78 °C furnished a yellow precipitate. After stirring for 30 min. 1.33 g (11.0 mmol) allyl bromide (**2**; n=1) were slowly added. The precipitate dissolved already at -78 °C (in contrast to the addition of bromides **2**; n=2,3). The orange red solution was warmed to room temperature within 12 h and worked up as described for **4** (n=1). The crude product, obtained in quantitative yield (2.15 g), consisted of a mixture of **4** (n=1) and **3** in a ratio 68:32 (^{1}H nmr, 60 MHz, $CDCl_3$). Addition of n-pentane yielded 210 mg (14%) amide **3** as yellowish precipitate. Whereas 1.54 g (65%) **4** (n=1) were isolated from the solution by Kugelrohr destillation with b.p. 45 °C/ $2 \cdot 10^{-2}$ Torr, the precipitate furnished 195 mg (13%) **3** on sublimation at 80 °C/$5 \cdot 10^{-2}$ Torr, colorless crystals, m.p. 83 °C.

IR (film) (cm^{-1}): 3330, 3150, 3080, 3020, 1675, 1625. ^{1}H nmr (400 MHz, $CDCl_3$): 1.65 (m, 3H, 5-Me), 2.13 (m, 3H, 1-H_a, 1'-H), 2.27 (m, 1H, 1-H_b), 2.56 (m, 1H, 2-H), 4.99-5.04 (m, 2H, 3'-H_a, 3'-H_b), 5.31 (ddq, 1H, 3-H), 5.49 (ddq, 1H, 4-H), 5.74 (m, 1H, 2'-H), 5.96, 6.41 (s, 2H, -NH_2);
J (Hz): $J_{5.4}$=6.30, $J_{5.3}$=1.50 Hz, $J_{1a.1b}$=14.40, $J_{1a.2}$=8.55, $J_{1'.2'}$=7.05, $J_{1b.2}$=5.85, $J_{2.3}$= 7.95, $J_{2.4}$=1.10, $J_{2.2'}$=1.00, $J_{3a'.2'}$=16.95, $J_{3b'.2'}$=10.30, $J_{3.4}$=15.30. -
$C_9H_{15}NO$ (153.2) Calc.: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.50; H, 9.67, N, 9.02.

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