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The Asymmetric Michael Reaction Involving Chiral Imines: Use of Acrylonitrile as Acceptor and Subsequent Functionalization of the Adducts

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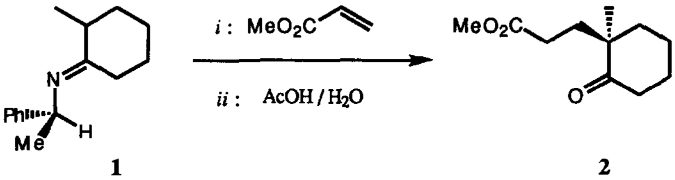
Key words : asymmetric Michael addition, chiral imines, Wittig reaction, epoxy-silanes, triazole formation.

Abstract : Condensation of chiral imines 1 and acrylonitrile led to adduct (R)-6 with an ee≥ 95 %. This adduct has then been converted into chiral synthons 9, 11, 12 and 17.

We have established that chiral imines, derived from *racemic* 2-alkylcyclanones and optically active 1-phenylethylamine, add to electrophilic alkenes leading, after hydrolytic work-up, to 2,2-dialkylcyclanones with a high degree of regio- and stereoselectivity. Thus, for example, addition of imine **1** to methyl acrylate gave adduct (*R*)-**2** with a good overall yield (85 %) and an excellent selectivity (92 % ee).[1]



In connection with the synthesis of various terpenes, we were recently interested to the subsequent functionalization of the Michael adducts of type **2**, at the level of the keto group, for example through an olefination reaction [**2**→ **5**, **6**→ **9**], or by carbonyl homologation [**6**→ **12**].

However, we have found that addition of an excess of methylenetriphenylphosphorane **3**, generated from the corresponding phosphonium bromide and potassium *tert*-amylate in toluene, to **2** (1 h, 20 °C) led exclusively in 55 % yield to bridged compound **4**,[2] instead of the expected methylene derivative **5**. Formation of the bicycle **4** clearly resulted from the base-promoted intramolecular Claisen-type condensation of **2**, followed by a double Wittig condensation on the resulting dione. It is worthy of note that this finding is in sharp contradiction with a recent report from a Korean group,[3] in which the authors claimed that reaction of the phosphorane **3** with keto-ester **2** afforded Wittig adduct **5** with a 52 % yield.[4]

$H_2C{=}PPh_3$

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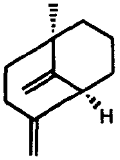

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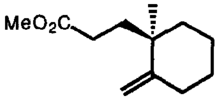

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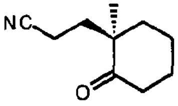
We reasoned that the preceding Claisen-type side-reaction would be minimized, by replacing keto-ester **2** by the corresponding keto-nitrile **6**. This new derivative was prepared by exposing imine **1** to acrylonitrile (a significantly more reactive Michael acceptor than methyl acrylate, since the reaction was achieved in 2 days at 20 °C). After hydrolytic work-up (20 % aqueous AcOH-THF, 2 h, 20 °C) adduct (*R*)-**6**[5], was isolated with a 75 % yield and ee ≥ 95 %. This ee, as well as the absolute configuration in adduct **6**, were determined by chemical correlation with the known keto-ester (*R*)-**2**[6] (dry HCl in MeOH, 60 °C, 24 h, then H_2O, 80 % yield). The use of acrylonitrile as acceptor in the present Michael reaction appears quite general; thus, for example, its addition to chiral imine **7**[7], derived from 2-methoxy-cyclohexanone, furnished adduct (*S*)-**8**[8] (55 % yield, 90 % selectivity).



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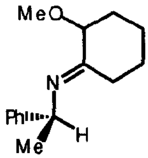

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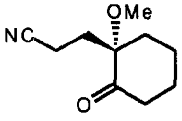

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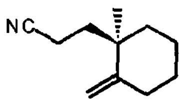
Disappointingly, addition of phosphorane **3**, generated with *n*-BuLi as base, to adduct **6** afforded the desired methylene derivative **9** in low yield (25 %). However, when *n*-BuLi was replaced by HNa in DMSO (20 °C, 3 h), this addition now proceeded straightforwardly, leading to methylene adduct **9**[9] with a 90 % yield.

This olefin would be next converted into aldehyde **12** by a stepwise sequence; nevertheless a more direct route to **12** would be the rearrangment of epoxide **11**, prepared by addition of sulfur ylide **10**[10] to **6**. This reaction led smoothly (2 h in refluxing THF, 65 % yield) to an equimolar mixture of epimeric epoxides **11**[11], easily separated by flash chromatography on silica gel. Lewis acid-induced rearrangement of these epoxides was then attempted under various conditions (BF_3-OEt_2; Et_2AlCl; $ZnCl_2$); however, only a minute amount (10-15%) of the desired aldehyde **12** was uniformly produced, along with several unidentified products.



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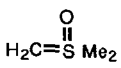

$H_2C{=}\overset{O}{\overset{\|}{S}}Me_2$

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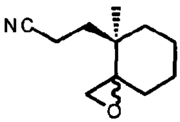

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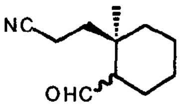

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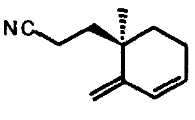
Quite surprisingly, the alternative rearrangement of epoxides **11**, upon heating in refluxing toluene (2 h) in the presence of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid, afforded a 1: 2 mixture of regioisomeric dienes **13** and **14** in 60 % yield, accompanied with 20 % of allylic alcohol **15**.

This alcohol clearly constitutes an intermediate in this reaction, since leading to these dienes under forced operating conditions.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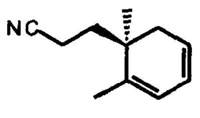
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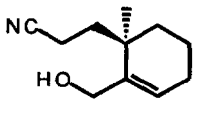
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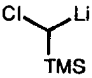
In view of the problems encountered in the Lewis acid-promoted transposition of epoxides **11**, we then decided to prepare the corresponding epoxy-silane **17**, since such derivatives are known to undergo clear-cut acidic rearrangement.[12] The latter derivative was obtained as a mixture of diastereomers, albeit with a modest yield (35 %), by condensing α-chloromethyltrimethylsilane lithium derivative **16**[13] to **6** (1 h in THF at -60 °C). To our delight, rearrangement of epoxy-silanes **17** proceeded cleanly : diols **18** were obtained by using 2*N* sulfuric acid at 20 °C, and aldehyde **12**[14] (as a 3: 1 mixture of diastereomers), by using trifluoroacetic acid in methanol (12 h, 20 °C, 90 % yield).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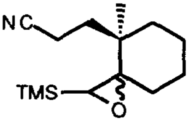
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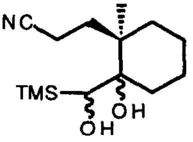
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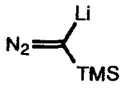
In order to improve the yield in the formation of epoxy-silane **17**, addition of trimethylsilyldiazomethane lithium anion **19**[15] to keto-nitrile **6** was next examined. However this addition (30 min in THF at -85 °C) led unexpectedly to the adduct **20**, which upon acidic treatment (1*N* HCl, THF) afforded triazole **21**[16] (42 % overall yield). Formation of compound **20** clearly resulted from an intramolecular 1,3-dipolar cycloaddition involving the pendant nitrile function in the primary adduct, as illustrated in **22**.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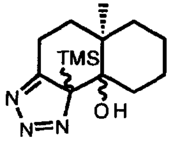
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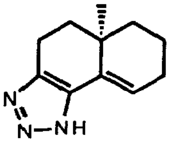
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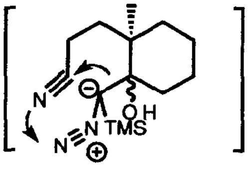
22

This work is pursued in our laboratory. Particularly the use of the preceding new, highly promising chiral synthons is currently under investigation.

References and Notes

1. d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron : Asymmetry*, **1992**, *3*, 459-505.
2. **4**: IR (film, cm^{-1}): ν: 3079, 2930, 1641, 1479; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 4.72 (d, J = 1.5 Hz, 1H), 4.70 (s, 1H), 4.65 (s, 1H), 4.55 (d, J = 1.5 Hz, 1H), 3.12 (broad s, 1H), 2.65 (m, 1H), 2.26 (dddd, J = 15.6, 10.9, 7.4, 3.5 Hz, 1H), 2.0-1.2 (m, 8H), 1.04 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 158.2 (C), 153.2 (C), 107.3 (CH), 101.9 (CH), 50.6 (CH), 42.1 (CH$_2$), 39.5 (CH$_2$), 36.6 (C), 35.8 (CH$_2$), 31.8 (CH$_2$), 28.3 (CH$_3$), 21.4 (CH$_2$)
3. Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O. ; Shimm, M. S.; Yun, J. S. *J. Org. Chem.*, **1994**, *59*, 1444-1456.
4. Having repeated under rigorously identical conditions the experiment described by the Korean authors[3] for the addition [2 + 3], we were unable to detect any amount of alkene **5**. Instead, products resulting from the intermolecular Claisen-type condensation between two molecules of keto-ester **2** were isolated.
5. **6**: $[\alpha]_D^{20}$ = -7.0 (c = 26, EtOH); IR (film, cm^{-1}): ν: 2940, 2238, 1703, 1451; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 2.50-2.20 (m, 4H), 2.00-1.60 (m, 8H), 1.12 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 213.0 (C), 119.3 (C), 46.8 (C), 37.6 (CH$_2$), 37.5 (CH$_2$), 32.7 (CH$_2$), 26.4 (CH$_3$), 21.3 (CH$_2$), 20.0 (CH$_2$), 11.1 (CH$_2$); Anal. Calcd. for C$_{10}$H$_{15}$ON: C, 72.70; H, 9.15; N, 8.47. Found: C, 72.60; H, 9.09; N, 8.38.
6. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.*, **1985**, *107*, 273-274.
7. Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.*, **1989**, *30*, 345-348.
8. **8**: $[\alpha]_D^{20}$ = -29.0 (c = 42, EtOH); IR (film, cm^{-1}): ν: 2238, 1710, 1452; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 3.14 (s, 3H), 2.66 (dd, J = 5.6, 12.5 Hz, 1H), 2.35-1.05 (m, 10H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 210.4 (C), 119.4 (C), 80. 6 (C), 49.9 (CH$_3$), 38.4 (CH$_2$), 35.6 (CH$_2$), 27.1 (CH$_2$), 26.2 (CH$_2$), 19.8 (CH$_2$), 10.1 (CH$_2$).
9. **9**: Colorless oil; bp 70 °C (0.1 Torr); $[\alpha]_D^{20}$ = +80.1 (c = 18, EtOH); IR (film, cm^{-1}): ν: 3092, 2940, 2238, 1638, 1452; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 4.81 (broad t, J = 1.6 Hz, 1H), 4.62 (t, J = 1.2 Hz, 1H), 2.20-2.00 (m, 3H) 1.60-1.25 (m, 9H), 1.03 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 152.2 (C), 120.3 (C), 108.7 (CH$_2$), 40.1 (CH$_2$), 38.9 (C), 32.8 (CH$_2$), 32.7 (CH$_2$), 28.0 (CH$_2$), 24.8 (CH$_3$), 21.7 (CH$_2$), 12.1 (CH$_2$).
10. Corey, E. J.; Chaykovsky, S. *J. Am. Chem. Soc.*, **1965**, *87*, 1353-1363.
11. **11**: *More polar isomer*: ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 2.80 (d, J = 4.2 Hz, 1H), 2.41(d, J = 4.2 Hz, 1H), 2.30 (m, 1H), 2.28 (t, J = 8.0 Hz, 2H), 1.90-1.45 (m, 9H), 0.82 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 120.1 (C), 61.6 (C), 50.7 (CH$_2$), 36.4 (CH$_2$), 35.9 (C), 32.7 (CH$_2$), 30.8 (CH$_2$), 24.0 (CH$_2$), 21.1 (CH$_2$), 19.0 (CH$_3$), 11.9 (CH$_2$). *Less polar isomer*: ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 2.73 (dd, J = 4.4, 1.5 Hz, 1H), 2.30-2.10 (m, 3H), 1.93 (m, 1H), 1.70-1.10 (m, 9H), 0.83 (s, 3H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 120.2 (C), 62.1(C), 49.0 (CH$_2$), 37.3 (CH$_2$), 35.6(C), 31.8 (CH$_2$), 30.9 (CH$_2$), 24.9 (CH$_2$), 20.8 (CH$_3$), 20.7 (CH$_2$), 11.7 (CH$_2$); Anal. Calcd. for C$_{11}$H$_{17}$ON: C, 73.74; H, 9.49; N, 7.82. Found: C, 73.84; H, 9.59; N, 7.86.
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13. Bufford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.*, **1977**, *99*, 4536-4537.
14. **12**: IR (film, cm^{-1}): ν: 2938, 2727, 1717, 1451; ^{1}H NMR (CDCl$_3$, 200 MHz) *Major isomer*: δ: 9.81 (d, J = 2.0 Hz, ,1H), 2.50-1.24 (m, 13H), 1.17 (s, 3H).*Minor isomer*: δ: 9.68 (d, J = 3.1 Hz, ,1H), 2.50-1.24 (m, 13H), 1.05 (s, 3H).
15. Schöllkopf, U.; Scholz, H.- U. *Synthesis*, **1976**, 271-272.
16. **21**: IR (film, cm^{-1}): ν: 3183 (broad), 3051, 2934, 1664, 1450; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 6.33 (t, J = 3.7 Hz, 1H), 2.85-2.70 (m, 2H) 2.20-2.05 (m, 2H), 1.90-1.20 (m, 7H), 1.04 (s, 3H); ^{13}C NMR (CDCl$_3$, 50MHz) δ: 140.8 (C), 140.7 (C), 131.7 (C), 122.0 (CH), 37.6 (CH$_2$), 37.0 (CH$_2$), 33.5 (C), 25.4 (CH$_2$), 22.8 (CH$_3$), 18.3 (CH$_2$), 18.1 (CH$_2$); MS: m/z 189(M$^{+\cdot}$, 40), 174(100), 160(20), 132(36), 91(40).

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