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1,3-Dipolar addition of nitrones to symmetrically substituted allenes: for the determination of absolute configuration of chiral allenes by NMR spectroscopy

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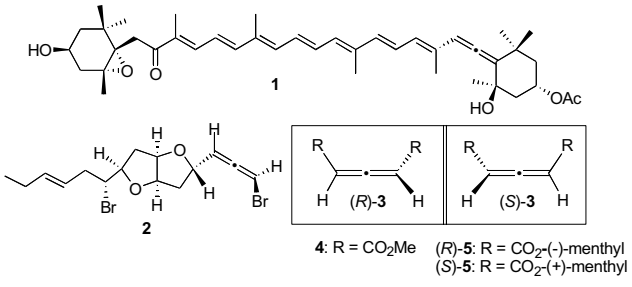
Abstract—5-Methyl-5-phenylpyrroline *N*-oxide was proved to be a useful 1,3-dipole for determining the absolute configuration of chiral allenes by means of NMR spectroscopy.

As a series of our studies on NMR methods to determine the absolute configuration of chiral secondary alcohols,[1] carboxylic acids,[2] and sulfoxides[3] by combining them with various types of chiral anisotropic reagents, we have recently started experiments directed toward elucidation of the stereochemistry of chiral allenes.

The allenic moieties are frequently found in natural products as exemplified by fucoxanthin **1**[4] and kumausallene **2**,[5] the chemical components of algae. Because an allene has an axis of symmetry, it can exist as enantiomer. There are several methods to elucidate the chirality of allenes, most of which are empirical,[6] excepting X-ray crystallography and CD.[7] We were interested in the simplest type of allenes **3** that can exist as (*R*)- and (*S*)-enantiomers. This paper describes our study on 1,3-dipolar addition of nitrile oxide and nitrones to allenes **4**[8] and **5**[9], which will lead to a new methodology for determination of absolute configuration of chiral allenes.



The regioselectivity of 1,3-dipolar addition to allenes has been documented,[10] and use of the dipolar reaction for absolute configuration study was prompted by Fukushi et al.[11] As the first candidate of the dipole, nitrile oxide **7** obtainable from commercially available 2-methoxy-2-phenylethanol (enantiomers and racemates are commercially available) via the nitro compound **6** was chosen. Use of (*R*)- and (*S*)-**6** would give the respective adducts **8** and comparison of the ^{1}H NMR chemical shifts of the diastereomers might lead to the absolute configuration of the allene, as in the case of the modified Mosher's method.[1]

A mixture of *rac*-**6** and *rac*-**4** in benzene was treated with phenyl isocyanate and triethyl amine. After 17 h at room temperature, 18% yield of **9** was chromatographically separated from the complex reaction mixture. Apparently, a double bond of the 'genuine adduct' **8** migrated during the reaction, which meant that information on the stereochemistry of the allene was lost (Scheme 1).

The 1,3-dipolar addition of nitrone **10** with *rac*-**4** was then attempted (78 °C, toluene, 24 h). The reaction gave also a messy mixture, from which an adduct **11**[12] (X-ray) was separated (13% yield) (Scheme 1). Because the yield

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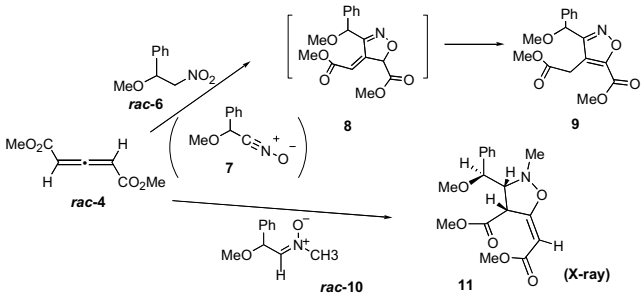
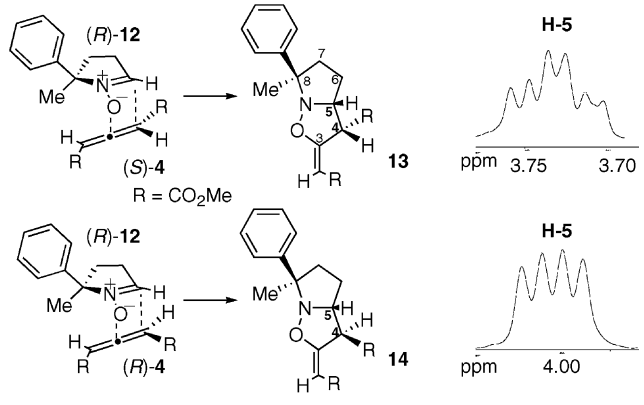


Scheme 1.

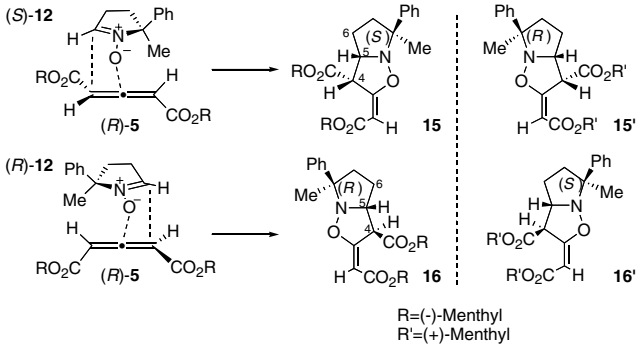
was too low and the other diastereomer at the methoxy(phenyl)methyl carbon was not obtained, we were forced to change the strategy.

The conformations of nitrile oxide **7** and nitrone **10** are flexible owing to their acyclic structures. If a cyclic nitrone is selected, it would be easier to consider the regio- and stereoselectivity of the dipolar addition. A commercially available *rac*-5-methyl-5-phenylpyrroline *N*-oxide **12**[13] was finally chosen as a 1,3-dipole. The supposed stereochemical course of the reaction between **12** and **4** is outlined in Scheme 2 (for convenience, only (*R*)-**12** is taken into consideration). The cyclization will take place from the *Si*-face of (*R*)-**12** to avoid the bulky phenyl group. The nitrone in turn will approach from the less hindered side of (*S*)-allene, that is, from the opposite side to the carbomethoxy group, giving the adduct **13**. Addition of (*R*)-**12** to (*R*)-allene will yield the diastereomer **14**. This prediction was substantiated by the following reaction.

A solution of *rac*-**4** and *rac*-**12** in benzene was heated at 40 °C for 24 h, when the TLC showed two spots. They were separated by HPLC, giving rise to diastereomers *rac*-**13** (24%) and *rac*-**14** (30%). The structures of **13** and **14** were confirmed by X-ray analysis.[12] Comparing **13** and **14**, one may notice that they are diastereotopic at C-4, reflecting the chirality of the allenes, and the chemical shifts of the H-4 may be affected by the phenyl group at C-8. In fact, H-4 of **13**, *cis* to the phenyl, appears at higher field (δ 4.76) than that of **14** (δ 4.93)



Scheme 2.



Scheme 3.

owing to the anisotropic effect of the benzene ring. We then noticed that the coupling patterns of H-5 were remarkably different between **13** and **14** [H-5 (**13**): ddd, $J = 9$, 9, 5 Hz, H-5 (**14**): dd, $J = 10$, 5 Hz]. (Dihedral angle H-4/H-5: 20° in **13** and 92° in **14**) (Scheme 2). The signal appears as an isolated one, and its coupling pattern together with the chemical shift may be used for determining the absolute configuration of allenes.

A chiral allene, di-(−)-menthyl (*R*)-allene-1,3-dicarboxylate **5**,[9] was reacted with *rac*-**12** under the same conditions, giving two diastereomers, **15** ($[\alpha]_D$ −262; 26%) and **16** ($[\alpha]_D$ +47; 41%). Their structures were confirmed by the NOE experiments (**15**; NOE 6β/Ph, 6β/5, 6β/4, 5/4. **16**; NOE 6β/5, 6α/4), which therefore led to the conclusion that **15** and **16** were the adducts of [(*S*)-**12** + (*R*)-**5**] and [(*R*)-**12** + (*R*)-**5**], respectively. Reaction of *rac*-**12** with (*S*)-**5**[9] afforded the enantiomers **15′** ($[\alpha]_D$ +263; 25%) and **16′** ($[\alpha]_D$ −46; 38%). Again, we observed that the chemical shift of H-4 was higher in **15** (**15′**) than in **16** (**16′**) and the coupling patterns of H-5 were ddd ($J = 9$, 9, 5 Hz) in **15** and dd ($J = 10$, 5 Hz) in **16** (Scheme 3).

The present results indicate that, if either of the enantiomers of **12** is available, it may be used to elucidate the absolute configuration of chiral allenes **3** by observing the coupling pattern of H-5. Very recently we succeeded in obtaining enantiomers of **12**, albeit in a small scale (HPLC separation), and their use in determination of the absolute configuration of various types of allenes is being studied.

Supporting information: Data for compounds **9**, **11**, **13**–**16**, **15′**, **16′** are reported in Ref. 14.

Acknowledgements

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12. CCDC 231996, 231997, and 231998 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
13. Purchased from Toronto Research Chemicals Inc.
14. *Experimental data*:
    Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (3H, s), 3.55 (3H, s), 3.60 (1H, d, $J = 17.2$ Hz), 3.73 (1H, d, $J = 17.2$ Hz), 3.92 (3H, s), 5.57 (1H, s), 7.26–7.36 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 52.0, 52.5, 57.3, 77.5, 117.4, 126.2, 128.1, 128.4, 137.3, 157.3, 157.5, 163.6, 169.3. HRMS(EI) m/z: 319.1051 (calcd for $C_{16}H_{17}NO_6$: 319.1056).
    Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 3.07 (3H, s), 3.47 (1H, dd, $J = 9.2$, 8.0 Hz), 3.67 (3H, s), 3.82 (3H, s), 4.17 (1H, d, $J = 8.8$ Hz), 4.81 (1H, dd, $J = 8.0$, 1.6 Hz), 5.47 (1H, d, $J = 1.6$), 7.29–7.39 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.2, 51.1, 52.3, 53.5, 56.2, 73.8, 81.2, 91.2, 127.9, 128.4, 138.4, 167.3, 168.5, 169.1. IR (liquid film) 2942, 1741, 1708, 1647, 1558, 1435, 1360, 1170, 1116, 1040, 763, 761 (cm^{-1}). HRMS(EI) m/z: 335.1387 (calcd for $C_{17}H_{21}NO_6$: 335.1369).
    Compound **13**: ^{1}H NMR (400 MHz, C_6D_6) δ 1.29 (1H, m), 1.57 (3H, s), 1.94 (1H, m), 1.95 (1H, m), 2.03 (1H, dd, $J = 18.6$, 10.6 Hz), 3.40 (3H, s), 3.49 (3H, s), 3.73 (1H, ddd, $J = 9.2$, 9.2, 4.7 Hz), 4.76 (1H, dd, $J = 8.8$, 1.6 Hz), 5.83 (1H, d, $J = 1.6$ Hz), 7.08–7.18 (3H, m), 7.36 (2H, d, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 26.2, 27.0, 34.1, 50.7, 51.7, 56.1, 64.9, 75.4, 90.0, 125.8, 127.3, 128.7, 144.6, 168.0, 168.1, 168.5. HRMS(EI) m/z: 331.1404 (calcd for $C_{18}H_{21}NO_5$: 331.1420).
    Compound **14**: ^{1}H NMR (400 MHz, C_6D_6) δ 1.14 (1H, dddd, $J = 13.6$, 10.0, 8.8, 1.6 Hz), 1.47–1.60 (1H, overlap), 1.55 (3H, s), 1.71 (1H, ddd, $J = 13.2$, 10.4, 10.4 Hz), 1.99 (1H, ddd, $J = 13.0$, 8.6, 1.6 Hz), 3.36 (3H, s), 3.46 (3H, s), 4.00 (1H, dd, $J = 9.6$, 5.2 Hz), 4.93 (1H, br s), 5.78 (1H, br s), 7.04 (1H, m), 7.10 (2H, m), 7.38 (2H, d, $J = 8.0$). ^{13}C NMR (75 MHz, C_6D_6) δ 27.3, 30.8, 33.6, 50.7, 52.3, 59.0, 67.6, 76.3, 89.2, 125.8, 127.4, 128.8, 144.2, 168.2, 168.8, 169.0. HRMS(EI) m/z: 331.1443 (calcd for $C_{18}H_{21}NO_5$: 331.1420).
    Compound **15**: ^{1}H NMR (400 MHz, C_6D_6) δ 0.68–0.83 (2H, overlap), 0.82 (6H, d, $J = 6.8$ Hz), 0.89 (1H, overlap), 0.95 (3H, d, $J = 7.2$ Hz), 1.03 (1H, overlap), 1.05 (2H, overlap), 1.06 (3H, d, $J = 6.8$ Hz), 1.09 (3H, d, $J = 6.8$ Hz), 1.20 (3H, d, $J = 6.8$ Hz), 1.25 (1H, m), 1.38 (1H, overlap), 1.40–1.54 (2H, overlap), 1.47–1.59 (2H, overlap), 1.50 (1H, overlap), 1.59 (1H, overlap), 1.60 (3H, s), 1.63 (1H, overlap), 1.97–2.15 (2H, overlap), 2.11 (1H, overlap), 2.14 (1H, overlap), 2.17 (1H, overlap), 2.23 (1H, septd, $J = 7.0$, 2.6), 2.69 (1H, septd, $J = 7.0$, 2.4 Hz), 3.89 (1H, ddd, $J = 9.2$, 9.2, 4.8 Hz), 4.88 (1H, dd, $J = 8.0$, 2.0 Hz), 4.95 (1H, ddd, $J = 10.8$, 10.8, 4.4 Hz), 4.98 (1H, ddd, $J = 10.8$, 10.8, 4.4 Hz), 5.89 (1H, dd, $J = 2.0$, 0.8 Hz), 7.10 (1H, m), 7.17 (2H, m), 7.40 (2H, d, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, C_6D_6) 16.8, 17.0, 20.8, 21.2, 22.2X2, 23.6, 24.1, 26.0, 26.6, 26.7, 27.1, 31.4, 31.8, 34.3, 34.5, 34.6, 41.0, 41.5, 47.4, 47.5, 56.4, 64.9, 73.4, 74.9, 75.4, 90.9, 125.9, 127.3, 128.7, 144.9, 167.1, 167.3, 168.1. HRMS(EI) m/z: 579.3894 (calcd for $C_{36}H_{53}NO_5$: 579.3924) $[\alpha]_D^{31} - 262.1$ (c 0.66, benzene).
    Compound **16**: ^{1}H NMR (400 MHz, C_6D_6) δ 0.65–0.88 (2H, overlap), 0,84 (3H, d, $J = 6.0$ Hz), 0.86 (3H, d, $J = 6.0$ Hz), 0.96 (1H, overlap), 1.00 (3H, d, $J = 6.8$ Hz), 1.02 (3H, d, $J = 7.2$ Hz), 1.03 (3H, d, $J = 6.8$ Hz), 1.05 (1H, overlap), 1.05 (3H, d, $J = 6.8$ Hz), 1.08 (1H, m), 1.12 (1H, m), 1.17–1.42 (2H, overlap), 1.20 (1H, overlap), 1.44–1.62 (2H, overlap), 1.47 (1H, overlap), 1.50 (1H, overlap), 1.57 (1H, overlap), 1.57 (3H, s), 1.58 (1H, overlap), 1.64 (1H, overlap), 1.75 (1H, ddd, $J = 13.2$, 10.2, 10.2 Hz), 2.00 (1H, ddd, $J = 13.1$, 8.9, 1.3 Hz), 2.15 (1H, overlap), 2.19 (1H, overlap), 2.24 (1H, m), 2.49 (1H, septd, $J = 7.0$, 2.6 Hz), 4.01 (1H, dd, $J = 9.6$, 4.8 Hz), 4.99 (1H, br s), 5.06 (2H, ddd, $J = 10.7$, 10.7, 4.3 Hz), 5.78 (1H, br s), 7.10 (1H, m), 7.17 (2H, m), 7.42 (2H, d, $J = 8.4$ Hz). ^{13}CNMR (100 MHz, C_6D_6) δ 16.5, 17.2, 20.9, 21.1, 22.18, 22.20, 23.5, 24.2, 26.2, 27.0, 27.4, 30.9, 31.5, 31.6, 33.7, 34.5, 34.6, 40.8, 41.8, 47.2, 47.4, 59.8, 68.2, 73.2, 75.1, 76.2, 89.6, 125.8, 127.5, 128.7, 144.5, 167.4, 168.1, 168.9. HRMS(EI) m/z: 579.3912 (calcd for $C_{36}H_{53}NO_5$: 579.3924) $[\alpha]_D^{31}$ +46.8 (c 1.02, benzene).
    Compound **15′**: $[\alpha]_D^{31}$ +262.6 (c 0.89, benzene) HRMS(EI) m/z: 579.3966 (calcd for $C_{36}H_{53}NO_5$: 579.3924) ^{1}H NMR spectrum was identical with that of **15**.
    Compound **16′**: $[\alpha]_D^{31}$ −46.4 (c 1.13, benzene) HRMS(EI) m/z: 579.3972 (calcd for $C_{36}H_{53}NO_5$: 579.3924) ^{1}H NMR spectrum was identical with that of **16**.