cis-3,4-Dichlorocyclobutene as a Versatile Synthon in Organic Synthesis. Rapid Entry into Complex Polycyclic Systems with Remarkably Stereospecific Reactions**

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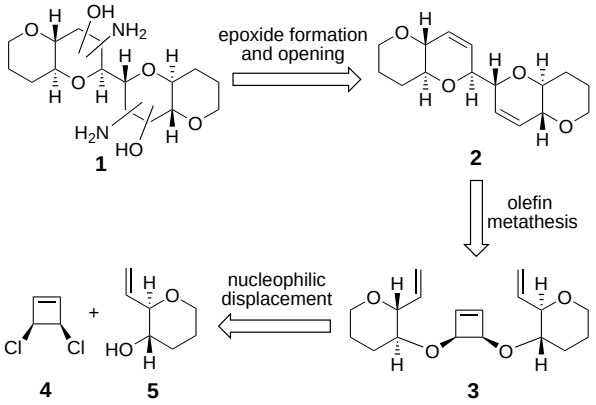
The frequent natural occurrence and wide-ranging biological activities of cyclic polyether-type structures has stimulated considerable efforts directed toward their synthesis.[1] Of particular interest are the aminoglycoside antibiotics represented by apramycin[2] and the marine neurotoxins represented by maitotoxin.[3] The former is of current interest by virtue of its RNA-binding properties,[2] whereas the latter constitutes a formidable synthetic challenge owing to its unprecedented molecular complexity and size. Functionalized polyether structures of type **1** (Scheme 1) embody



Scheme 1. Retrosynthetic analysis of structures of type **1**.

some of the key features found in these natural products, and as such they became targets in our investigations directed toward such complex molecular architectures. Herein we wish to report an expedient entry into these systems from readily available starting materials by means of a series of stereospecific nucleophilic substitutions and an olefin metathesis reaction.

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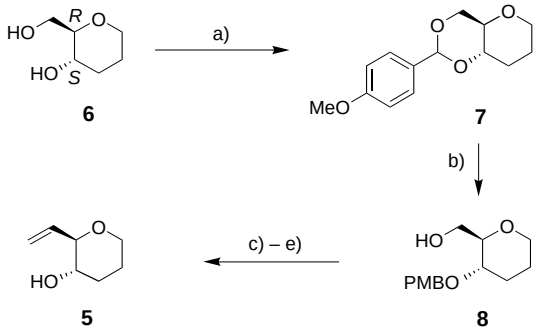
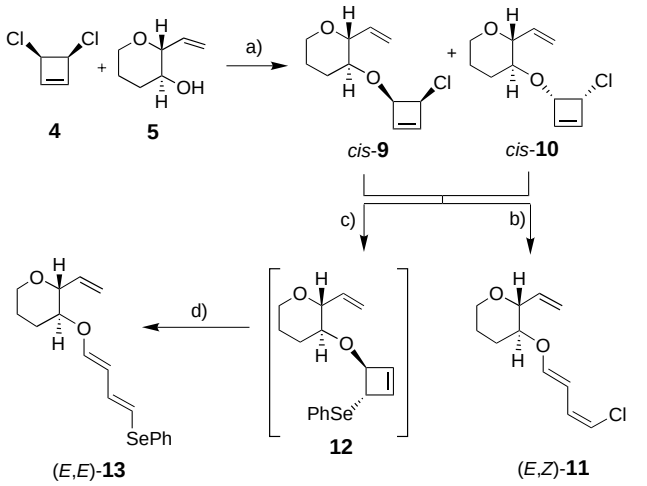
cis-3,4-Dichlorocyclobutene (**4**, Scheme 1) is a readily available building block whose synthetic utility remains largely unexplored despite the early and elegant mechanistic studies of Kirmse et al.[4] which pointed out its potential to undergo highly stereospecific displacement reactions. It was our intention to connect this simple synthon **4** to complex structures such as **1** through an expedient and stereospecific route. Scheme 1 outlines the retrosynthetic plan devised to accomplish this goal. Thus it was anticipated that structures of type **1** could be derived from diolefin **2** by epoxidation, followed by nucleophilic opening of the resulting epoxides. Whereas stereospecificity during the epoxide openings was highly desirable, random formation of these moieties was preferred, at least initially, for optimal molecular diversity. Diolefin **2** could, in turn, be obtained by tandem ring opening/ring closing olefin metathesis of cyclobutene derivative **3** (see Table 1 for physical properties) whose origin from *cis*-3,4-dichlorocyclobutene (**4**) and the hydroxytetrahydropyran system **5** was evident. Such a route constitutes a rapid and flexible access to complex molecular frameworks, which could easily be modified to produce tailor-made intermediates for total synthesis or compound libraries for biological screening purposes.

This strategy proceeded smoothly and, most importantly, revealed a number of interesting reactivity patterns and synthetic opportunities beyond the intended pathway. Hydroxytetrahydropyran **5** was prepared in enantiomerically pure form from **6** by a modification of a previously published sequence.[5] Thus, benzylidine formation followed by regioselective reduction with DIBAL-H, Swern oxidation, Wittig olefination, and DDQ-induced deprotection converted **6** into **5** in good overall yield (Scheme 2).

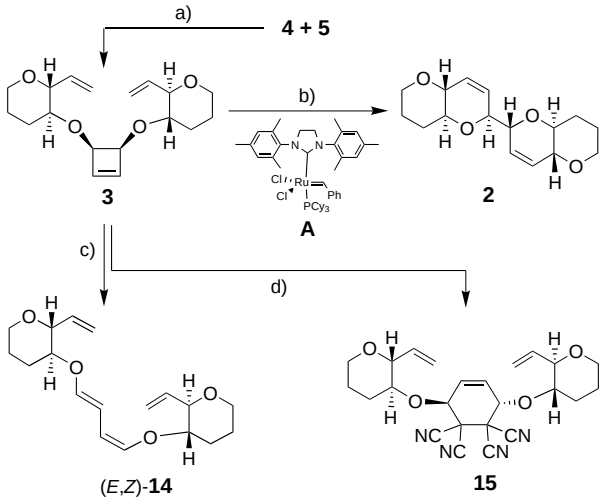


Scheme 2. Synthesis of **5**. Reagents and conditions: a) $MeOC_6H_4CH_2(OMe)_2$ (1.1 equiv), CSA (1.1 equiv), MeCN, 25 °C, 10 h, 82 %; b) DIBAL-H (3.0 equiv), THF, −40 °C, 5 h, 80 %; c) $(COCl)_2$ (1.1 equiv), DMSO (1.1 equiv), Et_3N (1.2 equiv), CH_2Cl_2, −78 °C, 25 °C, 2 h, 91 %; d) CH_3PPh_3Br (1.1 equiv), NaHMDS (1.1 equiv), THF, 0 →25 °C, 1 h; then aldehyde, 25 °C, 6 h, 75 %; e) DDQ (1.2 equiv), CH_2Cl_2:H_2O (10:1), 25 °C, 1 h, 95 %. CSA = 10-camphorsulfonic acid; DIBAL-H = diisobutylaluminum hydride; DMSO = dimethyl sulfoxide; NaHMDS = sodium bis(trimethylsilyl)amide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

The reaction of *cis*-3,4-dichlorocyclobutene (**4**) with hydroxy tetrahydropyran compound **5** was then explored. Exposure of **4** to 1.1 equivalents of the sodium alkoxide derived from **5** at 60 °C in THF resulted in the formation of the diastereomeric monosubstituted cyclobutene derivatives **9** and **10** (Scheme 3; 80 % yield, ca. 6:4 ratio). Heating of **9** or **10** or a mixture of the two in refluxing toluene resulted in a clean



Scheme 3. Displacement reactions of *cis*-3,4-dichlorocyclobutene (**4**) (*syn* S_N2' vs. *anti* S_N2'). Reagents and conditions: a) (*syn* S_N2') NaH (2.0 equiv), THF, 25 °C, 1 h; then **4** (1.1 equiv), 60 °C, 10 h, 80 %; b) (conrotatory) toluene, 110 °C, 3 h, 85 %; c) (*anti* S_N2') PhSeCl (1.2 equiv), NaH (2.2 equiv), DMF, 25 °C, 0.5 h, then **9** or **10**, 25 °C, 6 h, 85 %; d) (conrotatory). DMF = *N*,*N*-dimethylformamide.



Scheme 4. Tandem ring opening/ring closing metathesis reaction and conrotatory ring-opening Diels–Alder reaction of cyclobutene derivative **3**. Reagents and conditions: a) **5** (1.0 equiv), NaH (2.0 equiv), THF, 25 °C, 1 h; then **4** (0.5 equiv), 60 °C, 15 h, 85 %; b) **A** (Grubbs' catalyst; 5 mol %), toluene, 45 °C, 12 h, 80 %; c) toluene, 110 °C, 3 h, 90 %; d) TCNE (5.0 equiv), toluene, 110 °C, 3 h, 72 %.

conrotatory opening of the cyclobutene ring, thus leading to the *E*,*Z*-chlorodiene system **11** (85 % yield), whose geometry was confirmed by ^{1}H NMR spectroscopy (J_{cis} = 7.0 Hz, J_{trans} = 12.1 Hz).[4] This thermally induced reaction required relatively high temperatures and was in accordance with the expected *cis* stereochemistry of the cyclobutene derivatives **9** and **10**. Therefore, the displacement of chloride from **4** must have followed a *syn* S_N2' mechanism[4] in which the nucleophile approached the cyclobutene ring from the same side as the departing chloride ion. In contrast, the *anti* S_N2' attack[6] of the phenylselenyl anion on chlorobutene derivative **9** or **10** or a mixture of the two to furnish directly the *E*,*E*-phenylselenodiene **13** (85 % yield) is inferred on the basis of the known propensity of *trans*-cyclobutene derivatives to open through a conrotatory process at much lower temperatures than their *cis* counterparts.[7] No phenylselenocyclobutene derivative **12** was detected in this displacement reaction, which suggests both the *anti* S_N2' mode of reactivity of $PhSe^-$ with the chlorocyclobutenes **9** and **10** and the rapid conrotatory opening of the presumed *trans*-1,2-phenylselenocyclobutene **12** to the *E*,*E*-phenylselenodiene **13** at ambient temperature.

Treatment of **4** with two equivalents of the sodium alkoxide derived from **5** at 60 °C for 15 h gave **3** in 85 % yield (Scheme 4; Table 1). The cyclobutene derivative **3** was then exposed to the third-generation Grubbs' catalyst (**A**)[8] in toluene at 45 °C to afford the desired tetracycle **2** in 80 % yield. Despite close precedent for this olefin metathesis reaction with less sterically hindered substrates,[9] the first-generation Grubbs′ catalyst [$(Cy_3P)_2Cl_2Ru$=CHPh] failed to induce the desired reaction. To explore the chemistry of intermediates encountered on the way to the main target, a solution of compound **3** in toluene was heated at reflux in the absence and in the presence of tetracyanoethylene (TCNE). As expected from the *cis* stereochemistry of the cyclobutene derivative **3**, the *E*,*Z* diene system **14** was the only product of this conrotatory ring-opening reaction (90 % yield) in the absence of TCNE, whereas the C_2-symmetric Diels–Alder product **15** was formed exclusively in 72 % yield in the presence of TCNE, again as a consequence of the stereospecificity of the reactions.

The diolefin **2** was epoxidized in the desired random way by reaction with methyl(trifluoromethyl)dioxirane, which was generated in situ (CH_3CN, 0 → 25 °C),[10] to furnish all four possible epoxides **16**–**19** (Scheme 5) in 90 % total yield and in a ratio of approximately 1:1:1:1. Upon chromatographic separation, three of these epoxides (**16**, **17**, and **19**) crystallized

Table 1. Selected physical properties of compounds **3**, **16**, and **22**.

3: Colorless syrup; R_f = 0.37 (silica gel, Et_2O/hexane 1:1); $[\alpha]_D^{25}$ = +50.8 (c = 3.2, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2931, 2848, 1725, 1437, 1331, 1272, 1161, 1084, 990, 931, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.29 (m, 2H), 6.09 (ddd, J = 17.2, 11.7, 6.6 Hz, 1H), 6.02 (ddd, J = 17.2, 11.7, 6.6 Hz, 1H), 5.35 (dt, J = 17.2, 1.7 Hz, 2H), 5.19 (m, 2H), 4.65 (t, J = 2.4 Hz, 1H), 4.61 (t, J = 2.6 Hz, 1H), 3.93 (m, 2H), 3.64 (m, 2H), 3.38 (m, 2H), 3.23 (m, 1H), 3.11 (m, 1H), 2.20 (m, 2H), 1.66 (m, 4H), 1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.7, 141.8, 137.0, 136.6, 116.3, 116.2, 81.5, 81.4, 81.0, 80.8, 77.8, 77.2, 67.3 (2 C), 30.7, 30.6, 25.4, 25.2; HRMS (MALDI): calcd for $C_{18}H_{26}O_4$ [M+Na$^+$]: 329.1723, found: 329.1727

16: Colorless crystals; m.p. 146–149 °C (Et_2O/hexane 1:1); R_f = 0.55 (silica gel, Et_2O/hexane 4:1); $[\alpha]_D^{25}$ = +10.4 (c = 0.61, MeOH); IR (film): $\tilde{\nu}_{max}$ = 2942, 2855, 1440, 1266, 1135, 1092, 1023, 955, 837, 793, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.15 (d, J = 10.2 Hz, 1H), 3.99 (m, 3H), 3.63 (d, J = 4.4 Hz, 1H), 3.45 (m, 6H), 3.30 (d, J = 3.6 Hz, 1H), 3.07 (m, 2H), 1.98 (m, 2H), 1.72 (m, 4H), 1.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.8, 75.4, 72.1, 71.0, 69.4, 68.9, 68.8, 68.7, 55.2, 55.1, 52.3, 50.4, 29.2, 29.0, 25.6, 25.5; HRMS (MALDI): calcd for $C_{16}H_{22}O_6$ [M+Na$^+$]: 333.1309, found: 333.1302

22: Colorless crystals; m.p. 99–101 °C (Et_2O/hexane 1:1); R_f = 0.17 (silica gel, Et_2O); $[\alpha]_D^{25}$ = +39.4 (c = 0.53, MeOH); IR (film): $\tilde{\nu}_{max}$ = 3412, 2931, 2860, 2096, 1325, 1261, 1090, 1043, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.38 (d, J = 10.6 Hz, 1H), 4.24 (t, J = 3.4 Hz, 1H), 4.00 (m, 4H), 3.85 (dd, J = 5.5, 4.0 Hz, 1H), 3.71 (d, J = 10.6 Hz, 1H), 3.50 (m, 6H), 3.14 (d, J = 6.2 Hz, 1H), 2.94 (d, J = 4.7 Hz, 1H), 2.10 (m, 1H), 2.00 (m, 1H), 1.74 (m, 4H), 1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 76.6, 75.4, 75.2, 72.5, 70.8, 68.4 (2C), 67.1, 67.0, 66.8, 61.5, 60.6, 29.4, 29.1, 25.2, 25.1; HRMS (MALDI): calcd for $C_{16}H_{24}N_6O_6$ [M+Na$^+$]: 419.1649, found: 419.1634

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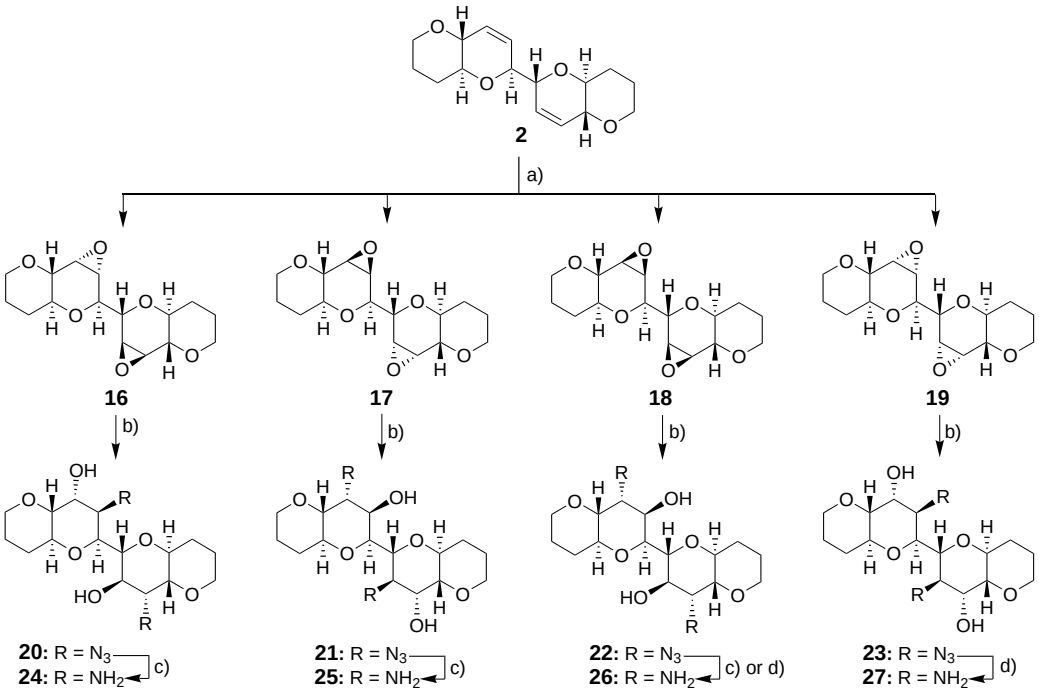


Scheme 5. Epoxidation of diolefin **2**, regiospecific epoxide openings and synthesis of dihydroxy-diamino compounds **24**–**27**. Reagents and conditions: a) Na_2EDTA (4×10^{-4} M (aq.), 0.3 mol%), CF_3COMe (40 equiv), $NaHCO_3$ (30 equiv), oxone (20 equiv), MeCN, 0 → 25 °C, 3 h, 90%; b) NaN_3 (3.0 equiv), NH_4Cl (3.0 equiv), MeOH/H_2O (7:1), 80 °C, 8 h, 88–92%; c) Et_3P (5.0 equiv), CH_3CN/H_2O (9:1), 25 °C, 48 h, 85–91%; d) H_2, Pd/C (10%), Et_3N (5.0 equiv), EtOH, 25 °C, 24 h, 77–81%. Na_2EDTA = ethylenediaminetetraacetic acid disodium salt.

from diethyl ether/hexane. The shown stereostructures were assigned unambiguously by means of X-ray crystallographic analysis (see Figure 1 for **16** and crystallographic data in ref. [11] for **17** and **19**).

Although the random formation of these epoxides (**16**–**19**) was not unexpected, their opening reactions with NaN_3 proved remarkably regio- and stereospecific. Thus, each of these diepoxides (**16**–**19**) opened up in a unique way (Scheme 5) in the presence of NaN_3 and NH_4Cl in MeOH/H_2O (7:1) at 80 °C and led stereospecifically to a single product (88–92% yield). In each reaction, the azide nucleophile apparently attacked from the less sterically hindered trajectory. As graphically depicted in Figure 1, the favorable trajectories (a and b) for the opening of diepoxide **16** led to the formation of diazide **20**. The unfavorable 1,2-diaxial interaction of the incoming azide nucleophile with the hydrogen at C5 (trajectory c) and the 1,2-pseudodiaxial interaction with the bulky group at C9 (trajectory d) were most probably responsible for the observed regiospecificity. Application of the same rationales to diepoxides **17**–**19** provides an explanation for the observed regiospecific outcome of these openings. The structures of these diazides were fully established on the basis of spectroscopic and X-ray crystallographic analysis of **20**, **21**, and **23** (see ORTEP drawing in Scheme 6 for **20** and crystallographic data in ref. [11] for **21** and **23**). The expected structure of diazodiol **22** was fully confirmed by HMQC experiments on the corresponding bis(*p*-bromobenzoate) derivative, which was easily prepared from diol **22** (4-bromobenzoyl chloride, Et_3N, 4-dimethylaminopyridine, 25 °C, 4 h, 93%). Each of the diazides obtained (**20**–**23**) was finally converted into the targeted diaminodiols[12] (**24**–**27**, Scheme 5) in good yield by either catalytic hydrogenation (10% Pd/C) or Et_3P/H_2O-facilitated reduction.

The observed exclusivity in the azide openings of epoxides **16**–**19** prompted us to examine this nucleophilic attack further. Thus, the use of less reagent (1.5 equiv NaN_3) in a shorter time (2 h) in the reaction of epoxide **16** resulted in the

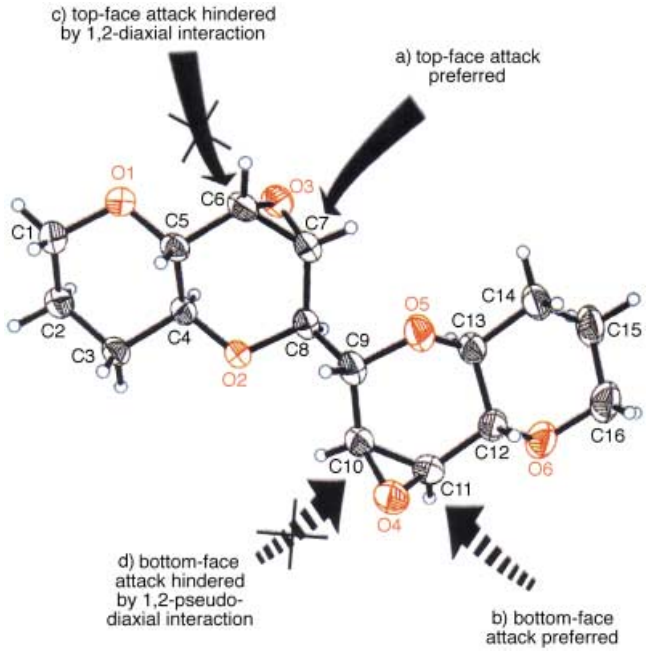
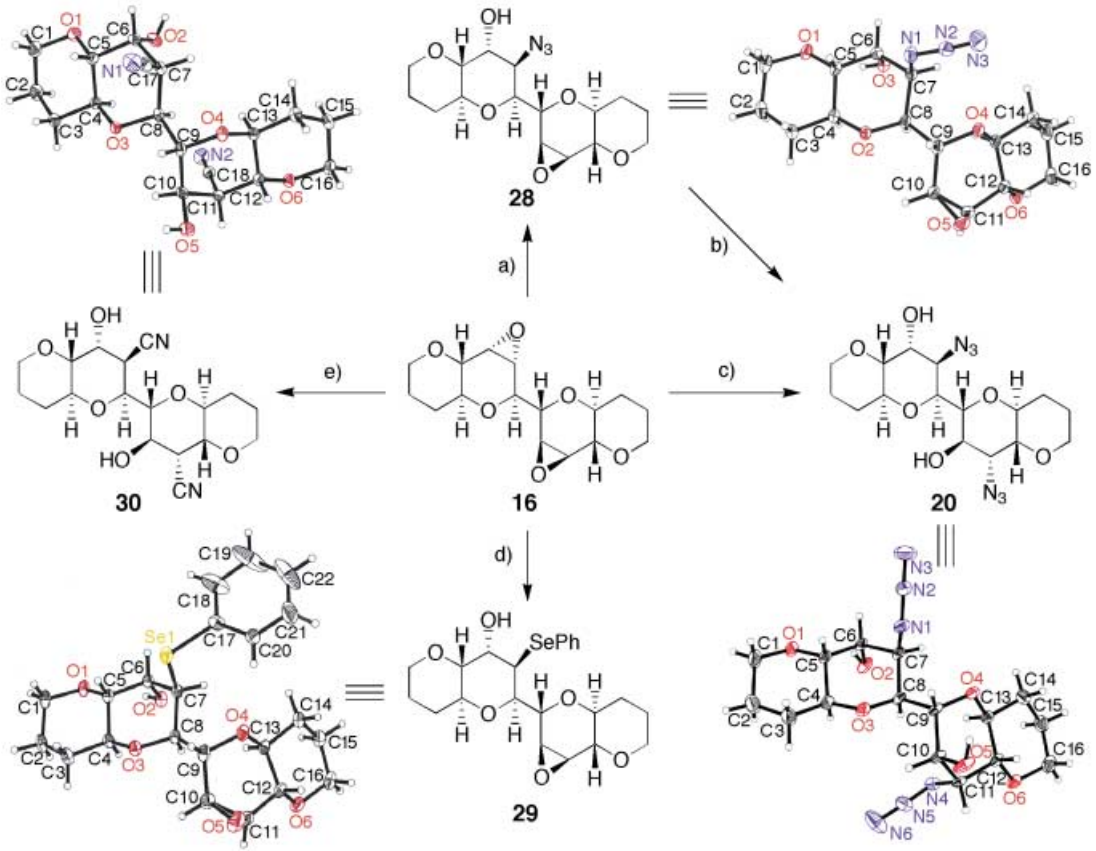


Figure 1. Postulated mechanistic rationale for the regiochemical outcome of the NaN_3 opening of diepoxide **16**. Trajectories a and b are preferred over trajectories c and d owing to less steric congestion. The conformation derived from the X-ray crystallographic analysis of **16** is used.



Scheme 6. Further regiospecific openings of diepoxide **16** with different nucleophiles, and ORTEP drawings of products. Reagents and conditions: a) NaN_3 (1.5 equiv), NH_4Cl (1.5 equiv), MeOH/H_2O (7:1), 80 °C, 2 h, 79 %; b) NaN_3 (1.5 equiv), NH_4Cl (1.5 equiv), MeOH/H_2O (7:1), 80 °C, 6 h, 90 %; c) NaN_3 (3.0 equiv), NH_4Cl (3.0 equiv), MeOH/H_2O (7:1), 80 °C, 8 h, 80 %; d) NaH (2.2 equiv), PhSeCl (2.2 equiv), DMF, 100 °C, 2 h, 79 %; e) Et_2AlCN (8.0 equiv), toluene, 0 °C, 0.5 h, 75 %.

regiospecific formation of mono-azide **28** in 79 % yield (Scheme 6). Thus the sequence of attack on this diepoxide was elucidated (trajectory a is more favorable than trajectory b; Figure 1), which confirms the steric factors that govern this reaction. The structure of **28** was confirmed by X-ray crystallographic analysis[11] (see ORTEP drawing in Scheme 6). Azide **28** was converted into the previously obtained diazide **20** by further reaction (6 h) with NaN_3 (1.5 equiv) at 80 °C (90 % yield). Increasing the steric demand in the reaction by employing the bulkier phenylselenyl anion [$PhSe^-$, generated in DMF from PhSeCl and NaH] led to the same regiochemical outcome as demonstrated by X-ray crystallographic analysis of the resulting monoselenide **29** (see ORTEP structure in Scheme 6). Finally, to probe the question of possible metal coordination effects in these epoxide openings, epoxide **16** was exposed to excess Et_2AlCN in toluene at 0 °C. The result of this experiment, in which complexation forces between the aluminum and the oxygen atoms of the substrate were expected to play a role, was again a highly regio- and stereospecific diepoxide opening, which led to dicyanodiol **30** in 75 % yield. The structure of **30** was proven by X-ray crystallographic analysis (see ORTEP structure in Scheme 6), which again underscores the dominant role of steric effects within these diepoxide structures in their behavior toward nucleophilic reagents.

In conclusion, we have demonstrated the versatility of *cis*-3,4-dichlorocyclobutene (**4**) as a useful building block in organic synthesis and devised a short and highly efficient route to complex and functionalized polyether systems starting from **4**. The methodology is expected to be useful in synthetic applications and in the construction of molecular diversity for biological screening.

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[1] For an adventure in total synthesis directed towards one of these compounds, brevetoxin B, see: K. C. Nicolaou, *Angew. Chem.* **1996**, *108*, 644 – 664; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 589 – 607.

[2] a) S. O'Connor, L. K. T. Lam, N. D. Jones, M. O. Chaney, *J. Org. Chem.* **1976**, *41*, 2087 – 2092; b) S. Perzynski, M. Cannon, E. Cundliffe, S. B. Chahwala, J. Davies, *Eur. J. Biochem.* **1979**, *99*, 623 – 628; c) R. Q. Thompson, E. A. Presti, *Antimicrob. Agents Chemother.* **1967**, *7*, 332 – 340; d) R. Ryden, B. J. Moore, *J. Antimicrob. Chemother.* **1977**, *3*, 609 – 613.

[3] a) M. Murata, T. Iwashita, A. Yokoyama, M. Sasaki, T. Yasumoto, *J. Am. Chem. Soc.* **1992**, *114*, 6594 – 6596; b) M. Murata, H. Naoki, T. Iwashita, S. Matsunaga, M. Sasaki, A. Yokoyama, T. Yasumoto, *J. Am. Chem. Soc.* **1993**, *115*, 2060 – 2062; c) M. Murata, H. Naoki, S. Matsunaga, M. Satake, T. Yasumoto, *J. Am. Chem. Soc.* **1994**, *116*, 7098 – 7107; d) M. Satake, S. Ishida, T. Yasumoto, *J. Am. Chem. Soc.* **1995**, *117*, 7019 – 7020; e) M. Sasaki, N. Matsumori, T. Maruyama, T. Nonomura, M. Murata, K. Tachibana, T. Yasumoto, *Angew. Chem.* **1996**, *108*, 1782 – 1785; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1672 – 1675; f) T. Nonomura, M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, T. Yasumoto, *Angew. Chem.* **1996**, *108*, 1786 – 1789; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1675 – 1678; g) W. Zheng, J. A.

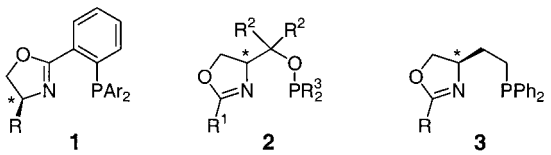
  1433-7851/01/4023-4444 $ 17.50+.50/0

DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 7946 – 7968.
[4] W. Kirmse, F. Scheidt, H.-J. Vater, *J. Am. Chem. Soc.* **1978**, *100*, 3945 – 3946.
[5] K. C. Nicolaou, C.-K. Hwang, B. E. Marron, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3040 – 3054.
[6] For previous reports of such reactions see: a) G. Stork, W. N. White, *J. Am. Chem. Soc.* **1956**, *78*, 4609 – 4624; b) G. Stork, A. F. Kreft III, *J. Am. Chem. Soc.* **1977**, *99*, 3850 – 3851; c) R. M. Magid, O. S. Fruchey, *J. Am. Chem. Soc.* **1977**, *99*, 8368 – 8370.
[7] G. Maier, A. Bothur, *Eur. J. Org. Chem.* **1998**, 2063 – 2072.
[8] For the preparation of this catalyst see: M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956.
[9] a) W. J. Zuercher, M. Hashimoto, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 6634 – 6640; for selected reviews on the olefin metathesis reaction, see: b) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18 – 29; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413 – 4450; d) T. J. Katz, *Adv. Organomet. Chem.* **1977**, *16*, 283 – 317.
[10] D. Yang, M.-K. Wong, Y.-C. Yip, *J. Org. Chem.* **1995**, *60*, 3887 – 3889.
[11] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. S CCDC-168813 – 168821. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[12] Interestingly, the spectroscopic data of diaminodiols **24** – **27** reveal the complexation with one molecule of either Et_3N or Et_3P, depending on the protocol used for their preparation (10% Pd/C, Et_3N or Et_3P/H_2O).

A New Class of Modular Phosphinite – Oxazoline Ligands: Ir-Catalyzed Enantioselective Hydrogenation of Alkenes**

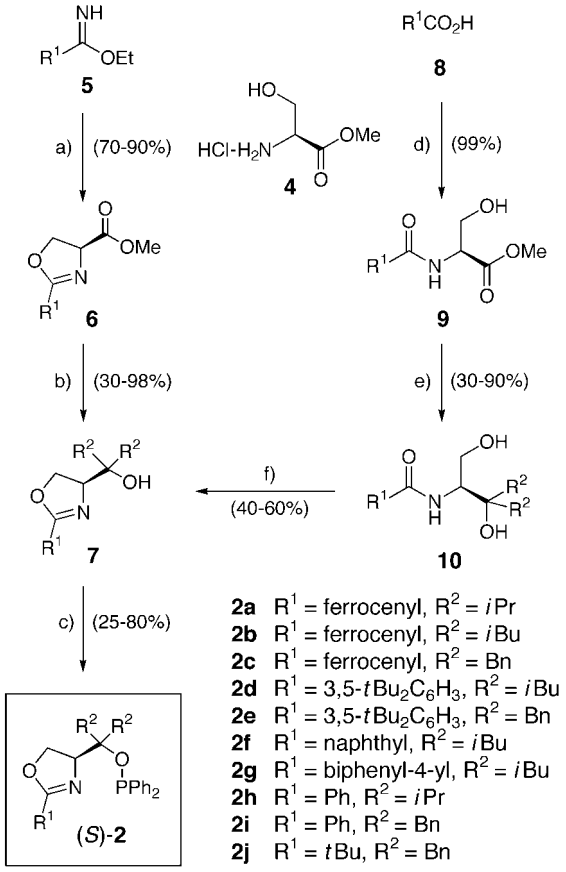
Jörg Blankenstein and Andreas Pfaltz*

Phosphinooxazolines **1** (phox ligands) have been successfully applied in many different enantioselective metal-catalyzed processes.[1] We have recently found that iridium – phox complexes are efficient catalysts for the enantioselective hydrogenation of unfunctionalized alkenes,[2] a class of substrates that gives unsatisfactory results with other catalysts.[3] The best enantioselectivities (up to 99% *ee*) have been observed for 1-alkyl-1,2-diaryl-substituted alkenes, while other alkenes such as monoaryl-1,2-dimethyl-substituted alkenes are converted with only moderate enantiomeric excesses. Here we report a new class of ligands, the phosphinite – oxazolines **2**, which induce high enantioselectivity with a much broader range of alkenes and, thus, significantly enhance the scope of Ir-catalyzed hydrogenation.



1 2 3

Both enantiomers of the phosphinite – oxazoline ligands **2** are readily prepared in three to four steps, starting from imidates **5** or carboxylic acids **8** and L-serine methyl ester hydrochloride (**4**) or the corresponding D isomer (Scheme 1). Special precautions had to be taken in the peptide coupling (step d) to avoid racemization.[4] The addition of Grignard reagents to **9** sometimes gave complex mixtures, so that in general the (hydroxymethyl)oxazolines **7** were preferentially synthesized by means of the imidate route.[5] The modular nature of **2** with its three permutable structural units (R^1, R^2, and the P-substituents) is an attractive feature of these ligands. Especially the selection of the R^1 group, which is derived from a carboxylic acid, is essentially unlimited.



Scheme 1. Synthesis of compounds **2** for which $R^3 = Ph$. a) **4**, $ClCH_2CH_2Cl$, reflux; b) R^2MgX, $-78\,^\circ C$; c) *n*BuLi, NEt_3, $ClPPh_2$, $-78\,^\circ C$; d) **4**, EDC, HOBT, CuCl, DMF; e) R^2MgX, $-78\,^\circ C$; f) (1) NEt_3, TsCl, (2) H_2O. EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, HOBT = 1-hydroxybenzotriazole.

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