Chiral Allyl Cations in Cycloadditions to Furan: Synthesis of 2-(1′-Phenylethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one in High Enantiomeric Purity**

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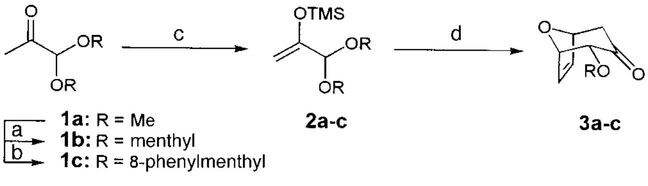
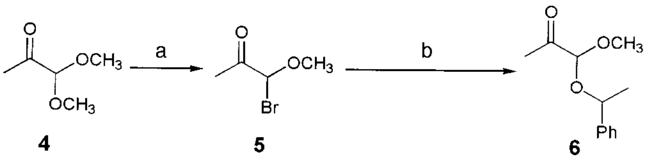
Asymmetric synthesis continues to be a major challenge of organic chemistry. In studies directed towards the total synthesis of marine natural products we required a simple route to enantiomerically pure 8-oxabicyclo[3.2.1]oct-6-en-3-ones, functionalized in the C_3 bridge. In the past a number of approaches to enantioenriched oxabridged seven-membered rings have been reported.[1, 2] However, fundamental problems remain, such as lack of generality. The direct introduction of a chiral center α to the carbonyl group of the C_3 bridge requires generation of a planar allyl cation in chiral space. The chiral carbocation[3] must be sufficiently reactive for π-facially selective, external capture by furan.

Lewis acid promoted ionization of silyl enol ether **2a** of pyruvic aldehyde dimethyl acetal (**1a**) in the presence of furan affords racemic 2-methoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (**3a**, Scheme 1).[4] We decided to introduce a chiral auxiliary into the acetal function. Initial attempts with (−)-menthol and (−)-8-phenylmenthol were unsatisfactory, and suffered from the drawback that the chiral alcohols could not easily be detached from the cycloadducts. Moreover, in the case of allylic acetal **2c**, (−)-8-phenylmenthol served as an expensive leaving group. We therefore prepared mixed chiral acetals from 1-phenylethanol, which is readily available in either enantiomeric form[5] (Scheme 2). Since 1-phenylethanol tends to form ethers and to racemize under S_N1 conditions such as prolonged contact with acids or on warming, the acetal was generated under basic conditions by deprotonation of the alcohol with *n*-butyllithium and S_N2 displacement of bromide ion from α-bromo ether **5**.[6]



Scheme 1. Exploratory work on asymmetric [4+3] cycloadditions. a) (−)-menthol, *p*TsOH (cat.), heptane, water separator, reflux, 60%; b) (−)-8-phenylmenthol, *p*TsOH (cat.), heptane, water separator, reflux, 6% (and 65% mixed acetal); c) LDA, TMSCl, THF, −78°C, quantitative; d) furan, TMSOTf, DCM, −78°C, 60–72%. *p*TsOH = *p*-toluene sulfonic acid, TMS = trimethylsilyl, OTf = trifluoromethane sulfonate, DCM = dichloromethane.



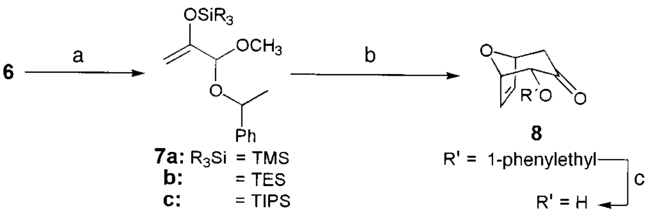
Scheme 2. Synthesis of mixed acetals **6** under basic conditions. a) AcBr, neat, room temperature, 89%; b) 1-phenylethanol, Et_2O, *n*BuLi, −20°C, then addition of **5** at −78°C, 92% (based on recovered 1-phenylethanol).

The resulting α-ketoacetal **6**[7] was transformed into the trialkylsilyl enol ethers **7a–c** (Table 1). The simple trimethylsilyl enol ether **7a** could not be purified, and cycloaddition to furan proceeded with variable diastereoselectivity and in irreproducible yield (Table 1, entry 1; Scheme 3). Triethylsilyl enol ether **7b** was more promising and therefore investigated in detail (Tables 2 and 3).

Table 1. Effect of the silyl capping substituent in enol ether **7a–c**.

Entry	7	Yield of 8 [%]	α:β[a]	*de* [%]
1	**a**	28–48	2.0:1 to 4.3:1	33–62
2	**b**	58	5.3:1	68
3	**c**	35	5.5:1	69

[a] For the definition of α and β see Figure 1.



Scheme 3. Lewis acid promoted diastereoselective [4+3] cycloaddition. a) LDA, R_3SiCl, THF, −78°C, 70–85%; b) furan, TMSOTf. For conditions see Tables 2 and 3; c) silica gel, DCM, 9 N HCl, reflux, 5 h, 60%. TES = triethylsilyl, TIPS = triisopropylsilyl.

Table 2. Effect of temperature on the cycloaddition of **7b** to furan.[a]

Entry	*T* [°C]	Yield [%] of **8**	α:β[b]	*de* [%]
1	−20	55	2.9:1	49
2	−78	58	5.3:1	68
3	−95	67	7.5:1	76

[a] Reaction time *t* = 10 min. [b] See Figure 1.

Table 3. Influence of solvent on the cycloaddition of **7b** to furan.

Entry	Solvent	*t* [min]	Yield [%] of **8**[a]	α:β[b]	*de* [%]
1	diethyl ether	90	10	1.2:1	10
2	THF	90	14	1.3:1	13
3	pentane	60	21	2.1:1	36
4	furan (neat)[c]	30	54	2.9:1	49
5	nitromethane	10	36	4.1:1	61
6	DCM	10	67	7.5:1	76
7	DCM/pentane[d]	10	37	8.2:1	78

[a] α-Methoxyketone **8** (R′ = Me) was formed as a by-product. [b] See Figure 1. [c] At −78°C. [d] At −110°C. All other experiments were carried out at −95°C.

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It is well known that the stereochemical outcome of an asymmetric transformation is temperature-dependent. Lowering the temperature often improves *de*'s. However, reaction rate and yield may decrease. In our case, a reduction in temperature from −20°C to −95°C increased the *de* of cycloadduct **8** from 2.9:1 to 7.5:1, while the chemical yield of cycloadduct **8** actually increased from 55 to a respectable 67% (Table 2, entry 2).[8] Solvent effects were also observed (Table 3). Oxygen-containing solvents, such as diethyl ether and THF, were unsatisfactory. In contrast dichloromethane (DCM) worked well, and a further decrease in solvent polarity (change from DCM to DCM/pentane) allowed a further reduction in temperature to −110°C, when a *de* of 78% was achieved. However, the chemical yield fell (Table 3, entry 7).

Subsequent to this exploratory work with racemic 1-phenylethanol (Tables 1–3), cycloadditions with enantiopure (*S*)-(−)-1-phenylethanol were equally successful. Thus, conversion of the α-bromo ether **5** into mixed acetal **6** and subsequent cycloaddition to form **8** do not affect the potentially sensitive asymmetric center of the chiral auxiliary. The adducts are readily separable on workup, and enantiopure α stereoisomer is obtained after chromatography.[9] Notably, carbon center C2 is conformationally constrained and proximate to carbon C1′ of the chiral auxiliary. Thus, diastereomeric differences are maximized.

Presumably, the observed stereoselectivity results from preferential shielding of one allyl cation π-face by the phenyl ring of the chiral auxiliary. In the transition state the reactive allyl cation is sandwiched between a 4π and a 6π system. An important intramolecular interaction is thought to exist between the silicon and the ether oxygen of the chiral auxiliary (Figure 1, broken line). The carbocation involved in the favored and disfavored path is structurally identical, but conformationally different. In the favored path the cation is thought to adopt the conformation which places the C1′-methyl group into the sterically least hindered position, remote from the TES group (Figure 1). The absolute configuration at carbon C2 of the major cycloadduct is in accord with this model.[9]

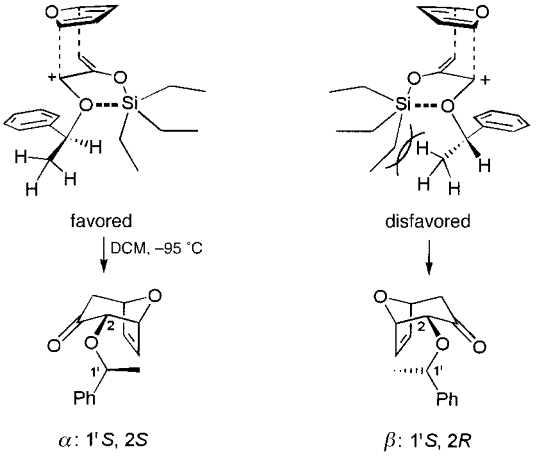

Figure 1. Possible routes to diastereoisomeric products in the cycloaddition of **7a** to furan.

We have developed a simple route with high chemical yields and *de's* to 2-(1′-phenylethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one. Simple chromatography affords enantiopure materials. 1-Phenylethanol is both a convenient chiral auxiliary and a protecting group. Currently, applications of this new diastereo- and enantioselective [4+3] cycloaddition in natural product synthesis[10] and extensions to related systems are being examined.

Experimental Section

General procedure for the asymmetric [4+3] cycloaddition of silyl enol ethers **7b** to furan: (−)-**7b** (12.9 g, 40.0 mmol; obtained from (*S*)-(−)-phenylethanol) and furan (2.80 mL, 2.72 g, 40.0 mmol) were dissolved in dry DCM (400 mL, 0.1 M). The solution was cooled to −95°C and TMSOTf (0.72 mL, 4.0 mmol, 0.1 equiv) was added dropwise. The reaction mixture was stirred for 10 min, poured into saturated $NaHCO_3$ solution, and extracted with DCM. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (ether/petroleum ether 1/3) afforded (−)-α (5.78 g, 23.7 mmol, 59.1% yield) and (−)-β (0.77 g, 3.15 mmol, 7.9% yield) as colorless solids (for a definition of α and β see Figure 1). (−)-α: m.p. 87–89°C; $[\alpha]_D = -166.7°$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 7.27-7.41$ (m, 5H, Ph), 6.38 (dd, $J = 5.8$ Hz, 1.6 Hz, 1H; H-7), 6.28 (dd, $J = 5.8$ Hz, 1.6, 1H; H-6), 4.94 (dd, $J = 4.8$ Hz, 1.6 Hz, 1H; H-5), 4.83 (q, $J = 6.4$ Hz, 1H, PhC*H*), 4.70 (dd, $J = 4.8$ Hz, 1.6 Hz, 1H; H-1), 3.94 (d, $J = 4.8$ Hz, 1H; H-2ax), 2.69 (dd, $J = 15.6$ Hz, 4.8 Hz, 1H; H-4ax), 2.33 (d, $J = 15.6$ Hz, 1H; H-4eq), 1.45 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 205.8$, 143.3, 134.5, 132.0, 128.6, 127.9, 126.4, 82.8, 80.2, 79.2, 78.3, 45.9, 24.2; IR ($CHCl_3$): $\tilde{\nu} = 3022$, 2980, 1724, 1452, 1328, 1264, 1176, 1144, 1100, 1076, 1044, 1008, 968; MS (70°C): m/z (%): 244 (2) [M^+], 216 (12), 215 (28), 161 (12), 148 (25), 140 (94), 105 (100), 97 (50), 77 (94); HRMS: calcd for $C_{15}H_{16}O_3$ 244.1100, found: 244.1100. (−)-β: m.p. 90–92°C; $[\alpha]_D = -93.9°$ ($c = 0.95$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 7.25-7.36$ (m, 5H, Ph), 6.39 (dd, $J = 6.4$ Hz, 1.7 Hz, 1H; H-7), 6.31 (dd, $J = 6.4$ Hz, 1.7, 1H; H-6), 5.06 (dd, $J = 4.8$ Hz, 1.7 Hz, 1H; H-1), 4.98 (d, $J = 4.8$ Hz, 1H; H-5), 4.76 (q, $J = 6.4$ Hz, 1H, PhC*H*), 4.08 (d, $J = 4.8$ Hz, 1H; H-2ax), 2.66 (dd, $J = 15.2$ Hz, 4.8 Hz, 1H; H-4ax), 2.35 (d, $J = 15.2$ Hz, 1H; H-4eq), 1.50 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 202.9$, 143.5, 134.7, 131.8, 128.5, 127.8, 126.4, 82.7, 78.9, 78.3, 77.1, 45.7, 24.0.

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[7] The α-ketoacetal **6** was isolated as a diastereoisomeric mixture. The compounds were not separated since the acetalic stereocenter is lost during generation of the siloxyallyl cation intermediate.

[8] Less than 0.1 equivalent of TMSOTf sufficed for this transformation; cf also ref. [4].

[9] With the Mosher ester of the deprotected cycloadduct (Scheme 3) and by comparison with an independently prepared sample of (−)-2-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-one: I. C. Rose, PhD thesis, University of Hannover, 1997.

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Neutron Diffraction Study of $[Nd(AlMe_4)_3] \cdot 0.5\,Al_2Me_6$ at 100 K: The First Detailed Look at a Bridging Methyl Group with a Trigonal-Bipyramidal Carbon Atom[**]

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Pentacoordinate carbon is an unusual entity. When it is observed, it exists in the form of a bridging alkyl group[1] or, in a few rare cases, as an interstitial atom in a metal cluster complex.[2] Although several examples of bridging alkyl groups have been structurally characterized,[3–15] the hydrogen atoms associated with such bridges have not always been located in the X-ray diffraction studies. We describe here the first example of a bridging methyl group structurally characterized with neutron diffraction[4] and show that it can adopt a trigonal-bipyramidal-like geometry.

The title compound **1** is the mixed-metal complex $[Nd(AlMe_4)_3]$ (isolated as a cocrystalite with Al_2Me_6),[8] which contains asymmetrical methyl bridges between neodymium and aluminum atoms. Pale purple-blue crystals of **1** were produced by the reaction of excess Al_2Me_6 with $[Nd(NMe_2)_3(LiCl)_3]$[8] and recrystallized from hexane. The transportation and mounting of the crystals for neutron diffraction was challenging because of the moisture and temperature sensitivity of the sample (it decomposes above −40°C).[16] The crystal was mounted in a specially designed anaerobic coldbox. A crystal with approximate volume 1.0 mm^3 was sealed in an aluminum container under a helium atmosphere and cooled to 100 K for neutron data collection. A total of 4535 reflections were scanned and refinement of the structure with 4013 independent F_o^2 values yielded final agreement factors of $R = 0.142$ and $R_w = 0.139$ based on 3σ data.[17] Despite the fact that these values are relatively high (due to the small size of the crystal and also possibly due to partial decomposition during the difficult crystal-mounting procedure), the final geometrical results (distances, angles, and their esd's) are quite respectable.

A molecular plot of the structure (Figure 1) shows the sixfold coordination of carbon atoms around neodymium. Each $AlMe_4$ unit is coordinated to the central Nd atom through two bridging methyl groups, which in turn are oriented such that two of their three H atoms are directed at the Nd atom. The coordination number around Nd is either six (if only Nd–C bonds are counted) or eighteen (if Nd···H interactions are included). Apparently, it is the steric unsaturation of the larger Nd^{III} atom rather than the enhanced Lewis

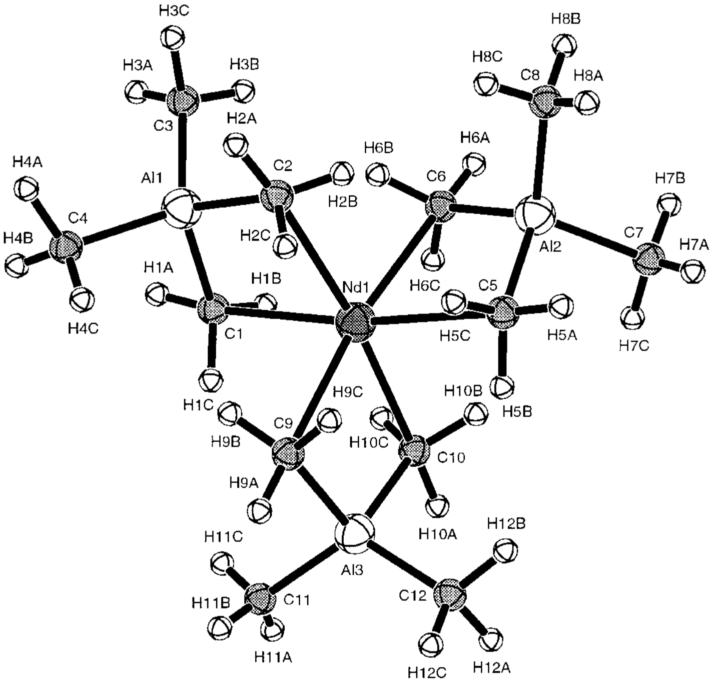

Figure 1. Stucture of $[Nd(AlMe_4)_3]$ as determined by single-crystal neutron diffraction. Each methyl group is oriented such that one hydrogen atom (labeled $H1_A$, $H2_A$, etc.) is essentially *trans* to the Nd atom. Average distances [Å] and angles [°]: Nd–C 2.598(11), Nd–H 2.649(13), Nd–Al 3.138(10), Al–C(bridge) 2.087(11), Al–C(terminal) 2.006(11), C–H_A 1.09(1), C–$H_{B,C}$ 1.08(1); Nd-C-H_A 173.8(8), H_B-C-H_C 107.4(9), Al-C-$H_{B,C}$ 123.2(9), Nd-C-Al 83.4(4), Nd-C-$H_{B,C}$ 80.3(4), Al-C-H_A 91.2(10), H_A-C-$H_{B,C}$ 102.2(14).

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