Building Blocks for the Stereocontrolled Synthesis of 1,3-Diols of Various Configurations

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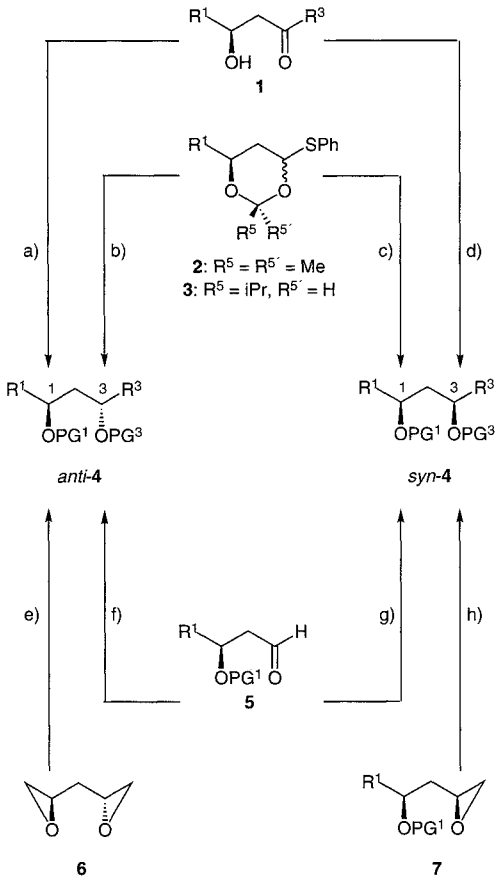
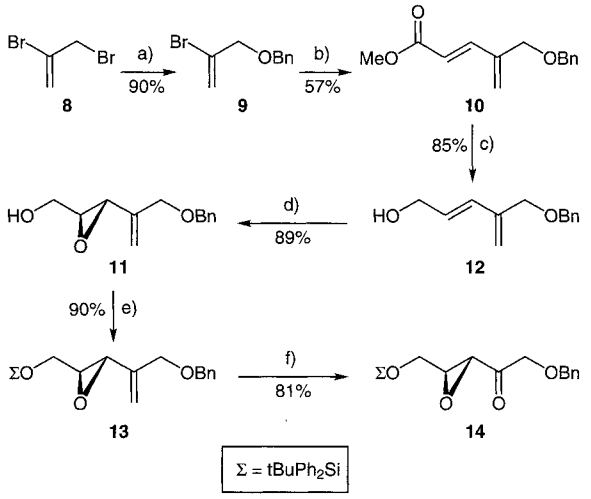
Abstract: A Sharpless epoxidation of the pentadienol **12** afforded the unsaturated epoxyalcohol **11** with 97.7% *ee*. Silylation of **11** and ozonolysis provided the epoxyketone **14**. A completely *anti*-selective reduction of **14** succeeded with $Zn(BH_4)_2$. It led to the epoxyalcohol **15** which was converted into the acetonide alcohols **21** and **23**, building blocks for enantiopure *anti*-1,3-diols. Alternatively, the same epoxyketone **14** and $cp_2Ti(III)Cl$ / 1,4-cyclohexadiene gave the β-hydroxyketone **16**. This compound was transformed into the acetonide alcohols **22** and **24**, building blocks for enantiopure *syn*-1,3-diols.

The stereoselective synthesis of 1,3,5,7,...-polyols has attained a level of considerable sophistication.[1] While larger targets abound, the preparation of the simplest representatives of this class of compounds, i. e. of stereodefined *anti*- or *syn*-1,3-diols, has lost none of its importance. This is because 1,3,5,7,...-polyols are often prepared from *anti*- or *syn*-1,3-diols and because in syntheses of 1,3,5,7,...-polyols one or several of their 1,3-diol subunits are obtained by methods developed for the obtention of the proper 1,3-diols themselves. Scheme 1 summarizes the more frequently used pathways to 1,3-diols or 1,3-diol subunits.



Scheme 1. *Standard syntheses of stereodefined 1,3-diols. a) Ref.* [3]*.- b) Ref.* [4,5]*.- c) Ref.* [6]*.- d) Ref.* [2]*.- e) Ref.* [10]*.- f) Ref.* [8]*.- g) Only possible starting from enantiomerically pure* **5***; ref.* [9]*.- h) Ref.* [11]*.*

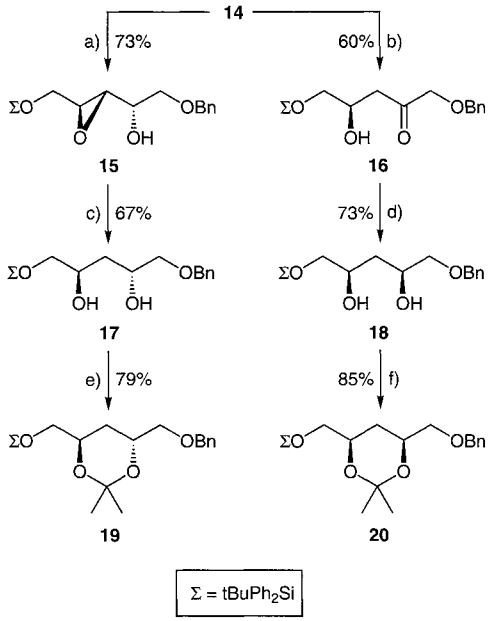
An important access to 1,3-diol(subunit)s is the diastereoselective reduction of β-hydroxyketones **1**: Perfect *syn*-selectivities are attained by the Narasaka / Prasad reduction of the derived diethylborinates[2] while good *anti*-selectivities originate from intramolecular hydride delivery methods.[3] The other 1,3-diol(subunit) syntheses of Scheme 1 are C–C bond forming reactions. The reductive lithiation of O,S-acetals **2** [4] or **3** [5] gives lithioethers which can be alkylated at dry-ice temperature providing the 1,3-diols **4** with *anti*-selectivity; alternatively, these lithioethers are epimerized at 0°C whereafter they react with alkylating agents so that they furnish 1,3-diols **4** exclusively as *syn*-isomers.[6,7] *O*-protected β-hydroxyaldehydes **5** are well suited for the chelation-controlled addition of organometallic reagents; a wide variety of *anti*-configurated 1,3-diols **4** can thus be obtained.[8] *Syn*-selective additions to *O*-protected β-hydroxyaldehydes **5** are not generally possible unless one exploits addition reactions with reagent control of diastereoselectivity.[9] Sequential ring-openings of the C_2-symmetric bisepoxide **6** or its enantiomer through organometallics constitute an elegant synthesis of homochiral *anti*-1,3-diols **4**.[10] Epoxide openings through organometallics which lead to *syn*-configurated 1,3-diols **4** are essentially those of Lipshutz' group which possess the general structure **7**.[11] By the work described in the present paper – the synthesis of two pairs **21/23** and **22/24** of acetonide-protected 1,3-diols (Scheme 4) – we offer useful starting materials other than **1-3** and **5-7** for the synthesis of enantiopure *anti*- and *syn*-1,3-diols. Compounds **21-24** were obtained as specified in Schemes 2-4.



Scheme 2. *a) $PhCH_2OH$ (1.0 equiv.), NaH (1.1 equiv.), THF, 0°C, 1 h; addition of* **8** *(45 mmol); → room temp., 4 h. b)* **9** *(20 mmol), $Pd(OAc)_2$ (4 mol-%), LiCl (1.0 equiv.), Bu_4NCl (1.0 equiv.), K_2CO_3 (2.5 equiv.), $H_2C{=}CH\text{-}CO_2Me$ (2.5 equiv.), DMF, 90°C, 2 h. c) DIBAL (2.2 equiv., 60 mmol), CH_2Cl_2, -78°C, 1 h. d) $Ti(OiPr)_4$ (54 mol-%), L-(+)-diisopropyltartrate (64 mol-%), CH_2Cl_2, -25°C, 15 min; addition of* **12** *(4.0 mmol), 10 min; tBuOOH (2.0 equiv.), molecular sieves 4Å, -20°C, 4 h; 97.7% ee. e) $tBuPh_2SiCl$ (1.2 equiv., 15 mmol), imidazole (1.05 equiv.), THF, 0°C, 3 h; room temp., 12 h. f) O_3, CH_2Cl_2, -78°C, 2.5 h; PPh_3 (1.5 equiv., 17 mmol), 2 h; → room temp., 12 h.*

First, the dibromopropene **8** [12] and sodium benzylalcoholate furnished benzyl ether **9** [13] in a Williamson reaction (90% yield; Scheme 2). As a secondary bromoolefin the ether **9** underwent a Heck coupling [14] with methyl acrylate. With the additives $Pd(OAc)_2$, Bu_4NCl, LiCl, and K_2CO_3 – as described by de Meijere *et al.* for couplings of *ortho*-dibromobenzene with acrylates in DMF [15] – we obtained the Heck product **10** in 57% yield. Compound **10** is a dienoic ester whose CO_2Me group was reduced with DIBAL chemoselectively. The dienol **12** resulted in 85% yield. Dienols which are 2,4-pentadien-1-ols can be epoxidized regio- and enantioselectively with the Sharpless cocktail [16] as reported a few times.[17] *Our* 2,4-pentadien-1-ol **12** undergoes such a regio- and enantioselective Sharpless epoxidation in the presence of $Ti(OiPr)_4$ and L-(+)-diisopropyltartrate, too. The epoxyalcohol **11** was isolated in 89% yield

and 97.7% *ee*.[18] Silylation of the OH group of **11** with *tert*-butyldiphenylsilyl chloride furnished the *O*-protected alkenyl-epoxide **13** in 90% yield. Its C=C bond was ozonolyzed. After treatment of the primary cleavage products with PPh_3 and chromatographic purification we obtained 81% of the epoxyketone **14**.



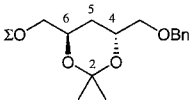
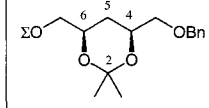
Scheme 3. *a) $Zn(BH_4)_2$ (1.7 equiv., 3.0 mmol), toluene, -80°C, 4 h. b) Zn powder (3.0 equiv.), cp_2TiCl_2 (1.1 equiv.), 1,4-cylohexadiene (15 equiv.), THF, room temp., 20 min; transferred dropwise to a solution of* **14** *(4.3 mmol) in THF; 60 min. c) Zn powder (3.0 equiv.), cp_2TiCl_2 (1.1 equiv.), 1,4-cylohexadiene (15 equiv.), THF, room temp., 20 min; transferred dropwise to a solution of* **15** *(1.5 mmol) in THF; 40 min. d) Et_3B (1.2 equiv.), MeOH, THF, 20 min, room temp., 1 h; addition of* **16** *(2.0 mmol); -78°C, 1 h; $NaBH_4$ (1.2 equiv.), 12 h. e) 2,2-Dimethoxypropane, camphor sulfonic acid (cat.), acetone, 0°C, 2 h (0.9 mmol scale). f) 2,2-Dimethoxypropane, camphor sulfonic acid (cat.), acetone, 0°C, 5 h (1.4 mmol scale).*

In the epoxyketone **14** we had to cleave the C–O bond α to the carbonyl group and to reduce the carbonyl group so that the new C–O single bond assumed either of the two possible orientations with respect to the preserved C_β–O bond. The order of these steps depended only on how one could best proceed to the 1,3-diol precursors **19** and **20**. An amendment to existing reduction methodology and an extension of it were required for realizing these goals (Scheme 3).

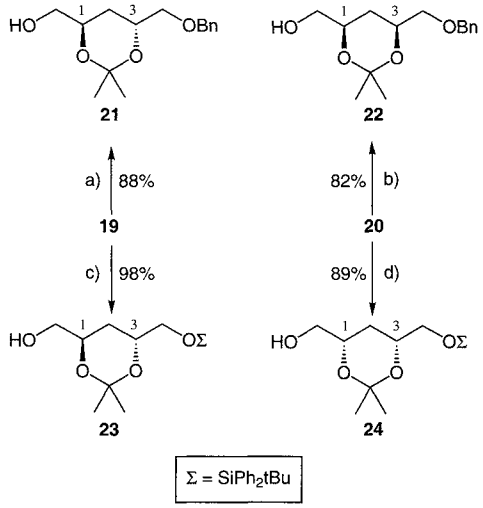
Anti-selective reductions of *trans*-configurated epoxy ketones akin to our substrate **14** were effected by Sato *et al.* [19] and by Fujii from the laboratory of Oshima and Utimoto [20] who both exploited chelation control of diastereoselectivity. The former researchers used $Zn(BH_4)_2$ in diethylether as the reductant and concomitantly as the chelating agent and observed a 95:5 *anti*:*syn* selectivity. The latter group used $NaBH_4$ in MeOH as the reductant and $CaCl_2$ as the chelating agent and found a 88:12 ratio of *anti* vs. *syn* product. Based on a literature report by Nakata, Oishi, *et al.* [21] on the solvent dependence of $Zn(BH_4)_2$-mediated chelation-controlled reductions of β-alkoxyketones and on paralleling results of ourselves [22] it was likely that reducing epoxyketones with $Zn(BH_4)_2$ *in diethylether* was sub-optimal for imposing *anti*-selectivity through chelation control. Indeed, treatment of epoxyketone **14** with $Zn(BH_4)_2$ *in toluene* – the optimum solvent of refs. [21, 22] – at -80°C gave the epoxyalcohol **15** (73%) as a *pure anti* isomer.[23] A regioselective opening of its epoxide ring was effected following RajanBabu's and Nugent's protocol:[24] exposure of the substrate to *in situ* prepared $cp_2Ti(III)Cl$ and to an excess of 1,4-cyclohexadiene. The *anti*-diol **17** thereby obtained was isolated in 67% yield. It was protected by an acid catalyzed transacetalization with 2,2-dimethoxypropane as acetonide **19** (79% yield).

For synthesizing the epimeric acetonide **20** (Scheme 3) the C–O bond α to the carbonyl group of the epoxyketone **14** was cleaved reductively by a reagent which has hitherto never been used for that purpose to the best of our knowledge: excess 1,4-cyclohexadiene and in-situ prepared $cp_2Ti(III)Cl$.[25,26] The β-hydroxyketone **16** was thus obtained (60% yield). After borination with Et_2BOMe and formation of a boron-bridged six-membered chelate it was reduced with $NaBH_4$ completely *syn*-selectively (73% yield; method: ref. [2]). The resulting *syn*-diol **18** was protected as acetonide **20** (85% yield).

Table 1. *Stereochemically relevant 300 MHz ^{1}H-NMR and 75 MHz ^{13}C-NMR data of acetonides* **19** *and* **20** *in $CDCl_3$ (δ values in ppm)*

Σ = tBuPh2Si	 **19** (IUPAC numbering)	 **20** (IUPAC numbering)
δ(4-H)	4.04	4.10
$\delta(5\text{-}H^A)$; $\delta(5\text{-}H^B)$	both 1.61	ca. 1.40; ca. 1.65
δ(6-H)	3.95	3.99
$J_{5\text{-}H(A),4}$; $J_{5\text{-}H(A),6}$	7.9 Hz; 7.9 Hz	11.7 Hz; 14.0 Hz
$J_{5\text{-}H(B),4}$; $J_{5\text{-}H(B),6}$	7.9 Hz; 7.9 Hz	2.5 Hz; 2.5 Hz
$\delta[2\text{-}(CH_3)_2]$	24.90 ; 24.99	19.69 ; 29.92
δ(C-2)	100.26	98.53

The stereostructures which we assign to the acetonides **19** and **20** were deduced from the ^{1}H- and ^{13}C-NMR data compiled in Table 1. The following stereochemistry-proving statements can be made: (1) The $\Delta\delta(^1H)$ values for the diastereotopic protons $5\text{-}H^A$ and $5\text{-}H^B$ and the differences between the vicinal coupling constants $J_{5\text{-}H(A),4\text{-}H}$ or $J_{5\text{-}H(A),6\text{-}H}$ on the one side and $J_{5\text{-}H(B),4\text{-}H}$ or $J_{5\text{-}H(B),6\text{-}H}$ on the other side are known to be small if existing at all in *anti*-acetonides (like in **19**) and relatively large in *syn*-acetonides (like in **20**).[27] (2) The $\Delta\delta(^{13}C)$ values for the diastereotopic methyl groups attached to C-2 are known to be negligible in *anti*-acetonides (like in **19**) but measure 10.4(0.7 ppm in *syn*-acetonides (like in **20**).[28] (3) The chemical shift of the acetal carbon C-2 is known to be (100.5 pm in *anti*-acetonides (like in **19**) and usually (99.5 ppm in *syn*-acetonides (like in **20**).[28]



Scheme 4. *a) Bu_4NF (1.1 equiv., 0.26 mmol), THF, 0°C → room temp, 4.5 h. b) Bu_4NF (1.5 equiv., 0.37 mmol), THF, 0°C → room temp., 18 h. c) Lithium naphthalenide (2.0 equiv., 0.34 mmol), THF, -78°C → room temp., 2 h. d) Lithium naphthalenide (2.0 equiv., 0.29 mmol), THF, -78°C → room temp., 40 min.*

Transforming the acetonides **19** and **20** into useful building blocks for *anti*- and *syn*-1,3-diols meant mono-deprotecting them (Scheme 4). The *tert*-butyldiphenylsilyl group was removed selectively by treating each

compound with an anhydrous solution of $Bu_4N^+F^-$ in THF. From the acetonide **19**, we thus obtained the 1,3-diol building block **21** (88%) and from the acetonide **20** the 1,3-diol building block **22**. Alternatively, the benzyl ethers both of acetonide **19** and its diasteromer **20** were cleaved with lithium naphthalenide.[29] Thereby we gained access to the 1,3-diol building blocks **23** (98%) and **24** (89%), respectively. The ^{1}H- and ^{13}C-NMR characteristics of the mono-deprotected acetonides **21/23** (**22/24**) resemble closely those (cf. Table 1) of their diprotected acetonide precursor **19** (**20**). This proves that all *anti/syn* relationships were fully preserved during the desilylations and debenzylations.

In summary, we present two novel building blocks **21** and **23** for the synthesis of *anti* 1,3-diols as well as two novel building blocks **22** and **24** for the synthesis of *syn* 1,3-diols. Conveniently, these building blocks **21-24** are derived from a single enantiopure progenitor, the epoxyalcohol **12**. Obviously, one could prepare the *enantiomeric* building blocks *ent*-**21** - *ent*-**24** by the same chemistry, too; *their* common progenitor would be the epoxide formed from the pentadienol **12**, *tert*-BuOOH, $(iPrO)_4Ti$, and D-(-)-diisopropyltartrate. **21-24** and *ent*-**21** - *ent*-**24** constitute a set of protected 1,3-diols of all possible configurations – 1*R*,3*R* (**21** and **23**), 1*R*,3*S* (**22** and *ent*-**24**), 1*S*,3*S* (*ent*-**21** and *ent*-**23**), and 1*S*,3*R* (*ent*-**22** and **24**) – with the possibility to choose between a benzylated and a *tert*-butyldiphenylsilylated species for any given configuration. The elaboration of these compounds into 1,3,5,7,...-polyols is currently under investigation in our laboratory.

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18. The *ee* of epoxyalcohol **12** was determined by gas chromatography on an enantiomerically pure stationary phase containing heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin. The racemic epoxyalcohol **12** (synthesized for comparison purposes by the method of Mihelich, E. D.; Daniels, K.; Eickhoff, D. I. *J. Am. Chem. Soc.* **1981**, *103*, 7690-7692) exhibited two baseline-separated peaks of equal height. The enantio-enriched sample of **12** caused a major GLC peak which coincided with the more slowly emerging enantiomer of racemic **12** and a minor peak which had the same retention time as the more rapidly emerging enantiomer of racemic **12**.
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23. *(2S,3R,4S)-1-(Benzyloxy)-5-(tert-butyldiphenylsiloxy)-3,4-epoxypentan-2-ol* (**16**): At -80°C $Zn(BH_4)_2$ (2.0 M solution in Et_2O, 1.48 ml, 2.95 mmol, 1.7 equiv.) was added dropwise during 5 min to a solution of the epoxyketone 14 (0.800 g, 1.74 mmol) in toluene (50 ml). The reaction mixture was quenched with MeOH (10 ml) after 4 h and allowed to warm to room temp. H_2O (10 ml) and HCl (2 M, 10 ml) were added. Extraction with tBuOMe (3 x 40 ml) and flash chromatography (eluent: petroleum ether:tBuOMe 10:1 → 1:1) gave **16** (0.581 g, 73%).- $[\alpha D]^{23} = -7.28$ ($c = 1.19$ in CH_2Cl_2).- IR: = 3435, 3070, 2930, 2860, 1725, 1590, 1470, 1425, 1390, 1365, 1270, 1200, 1110, 905, 825, 740, 705 cm^{-1}.- ^{1}H NMR (300 MHz): = 1.05 (s, tBu), 2.29 (br s, OH), 3.06 (dd, $J_{3,2} = 4.6$, $J_{3,4} = 2.5$, 3-H), 3.21 (ddd, $J_{4,5\text{-H(A)}} = 4.8$, $J_{4,5\text{-H(B)}} = J_{4,3} = 2.5$, 4-H), AB signal ($\delta_A = 3.57$, $\delta_B = 3.62$, $J_{AB} = 9.7$, in addition split by $J_{A,2} = 6.0$, $J_{B,2} = 4.0$, 1-H$_2$), AB signal ($\delta_A = 3.72$, $\delta_B = 3.90$, $J_{AB} = 12.1$, in addition split by $J_{A,4} = 4.6$, $J_{B,4} = 2.7$, 5-H$_2$), B part superimposes 3.83-3.91 (m, 2-H), extreme AB signal ($\delta_A = 4.57$, $\delta_B = 4.58$, $J_{AB} = 12.7$, 1'-H$_2$), 7.28-7.47 and 7.64-7.70 (2 m, 11 and 4 H, respectively, 3 x Ph).- Calcd. for $C_{28}H_{34}O_4Si$ (462.7): C 72.69, H 7.41; found: C 72.82, H 7.42.
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Page, B. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc. Perkin Trans. I* **1990**, 2403-2408; Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596-2599) worked less satisfactory in our hands.

25. We are indebted to Dr. Andreas Gansäuer (Universität Göttingen) for suggesting this method.

26. *(R)-1-(Benzyloxy)-5-(tert-butyldiphenylsiloxy)-4-hydroxy-2-pentanone* (**15**): Zn powder (0.819 g, 12.9 mmol, 3.0 equiv.) and cp_2TiCl_2 (1.18 g, 4.73 mmol, 1.1 equiv.) in THF (15 ml) were stirred at room temp. for 20 min. Residual Zn was allowed to settle. The supernatant solution was transferred dropwise via cannula in 40 min to a solution of the epoxyketone **14** (1.98 g, 4.30 mmol) and 1,4-cyclohexadiene (6.09 mL, 5.17 g, 64.6 mmol, 15 equiv.) in THF (20 ml). After another 20 min we quenched with HCl (2 M, 15 ml) and H_2O (20 ml). Extraction with tBuOMe (3 x 30 ml) evaporation of the solvent, and flash chromatography (eluent: petroleum ether:tBuOMe 5:1 → 1:2) yielded **15** (1.20 g, 60%).- $[\alpha_D]^{23}$ = 5.68 (*c* = 2.11 in CH_2Cl_2).- IR: = 3430, 3070, 2930, 2855, 1725, 1470, 1425, 1390, 1365, 1265, 1200, 1115, 1030, 825 cm^{-1}.- ^1H NMR (300 MHz): = 1.06 (s, tBu), AB signal (δ_A = 2.62, δ_B = 2.70, J_{AB} = 16.8, in addition split by $J_{A,4}$ = 4.4, $J_{B,4}$ = 8.1, 3-H_2), 2.82 (br s, OH), AB signal (δ_A = 3.60, δ_B = 3.65, J_{AB} = 10.0, in addition split by $J_{A,4}$ = 6.2, $J_{B,4}$ = 4.7, 5-H_2), 4.09 (s, 1-H_2), 4.22 (m_c, 4-H), 4.59 (s, 1'-H_2), 7.27-7.48 and 7.62-7.68 (2 m, 11 and 4 H, respectively, 3 x Ph).- Calcd. for $C_{28}H_{34}O_4Si$ (462.7): C 72.69, H 7.41; found: C 72.36, H 7.18.

27. (a) Cf. the experimental part of ref. [22b] and the data in footnote 19 of Menges, M.; Brückner, R. *Synlett* **1993**, 901-905.- (b) Priepke, H; Brückner, R. manuscript in preparation for *Liebigs Ann.*; Allerheiligen, S.; Brückner, R. manuscript in preparation for *Liebigs Ann.*

28. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948; Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.- (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100.

29. Previous use of this method: Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1471-1484.

Errata and Addenda

A Convenient Method for the Synthesis of Bis(trialkylphosphine)-Boranes Bearing Two Phospholanes. Morimoto, T.; Ando, N.; Achiwa, K. *Synlett* **1996**, 1211.

The following citation should be included in reference 6:

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