Horner–Wadsworth–Emmons Reactions as a Facile Entry to Biogenetic Key Substructures

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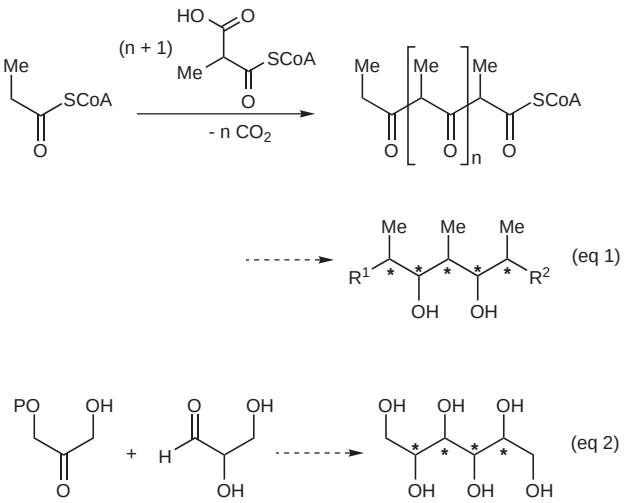
Abstract: One-pot Horner–Wadsworth–Emmons reactions are used to synthesize α,β-enones with two configurationally independent stereogenic centers. These intermediates are used for the construction of polyketide and monosaccharide fragments. In particular, novel approaches to the branched pentoses mycarose and arcanose are described

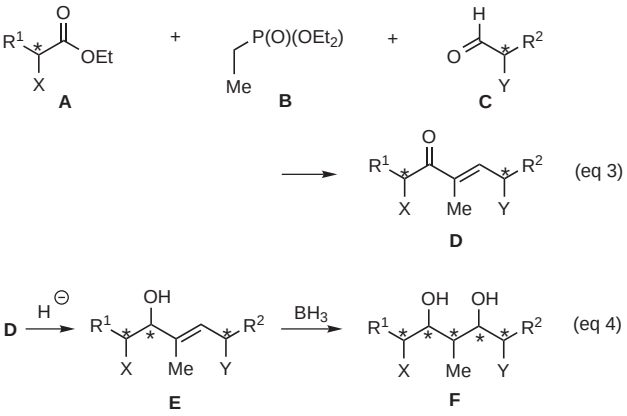
Keywords: polyketides, enones, carbonyl reduction, hydroboration, mycarose, arcanose

Biogenetic aldol-type C-C-connections are abundant in the formation of polyketide and carbohydrate polyol metabolites,[1] as illustrated in equations 1 and 2 in Scheme 1. In search of a non-aldol non-biomimetic pathway to these important structural patterns, we found that the venerable Horner–Wadsworth–Emmons (HWE) reaction[2] can be developed into a one-pot highly connective process (Scheme 2).[3] As shown in equation 3 in Scheme 2, an α-chiral ester A is connected across a phosphonate B with an α-chiral aldehyde C to form *E*-enone D, which has two stereogenic centers at C-1 and C-5, respectively, both with unambiguously defined configuration and fully independent from each other. X and Y can be heteroatoms or carbon appendages, most simply a methyl group. To capitalize on the synthetic potential of the enone moiety we sought for stereocontrolled reduction to convert D into the allylic alcohol E, which should then undergo stereocontrolled hydroboration to generate stereopentad F with defined stereochemistry (equation 4 in Scheme 2). To test the viability of this approach stereopentad **1**, and polypropionate fragments **3** and **4** were envisaged as lead structures. Additionally hexitol **2** was considered as a monosaccharide type target.

To prepare stereopentad **1** (Figure 1) which corresponds to the C1-C7-fragment **5** of monensin[4] and to the C5-C11-fragment **6** of lonomycin A (Figure 2),[5] ester **7** was converted into phosphonate **8** which was treated in situ with aldehyde **9** to give enone **10** *E*-selectively in good yield. TBS-deprotection and reduction with diborane furnished *syn*-alcohol **11** selectively, which was converted into acetonide **12** and subjected to hydroboration (Scheme 3). Stereopentad **1** was formed stereoselectively in high yield.



Scheme 1 Biogenesis of polypropionates and hexitols



Scheme 2 HWE-carbonyl reduction–hydroboration sequence

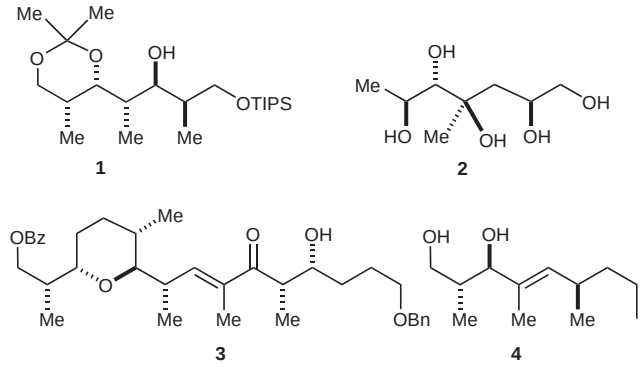


Figure 1

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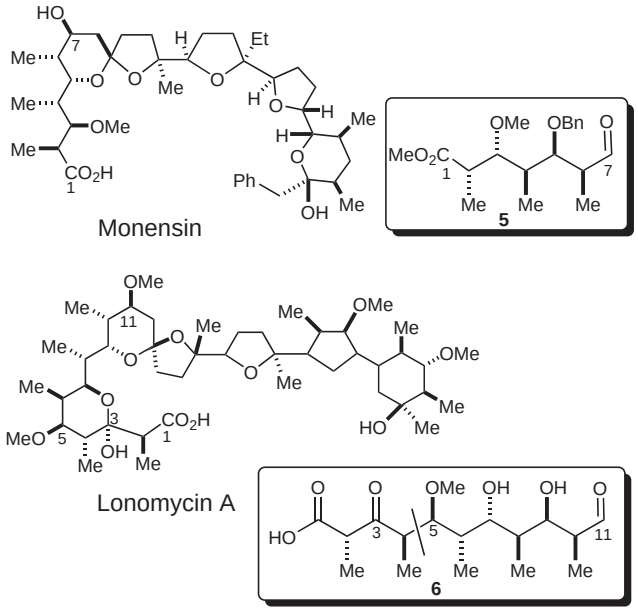
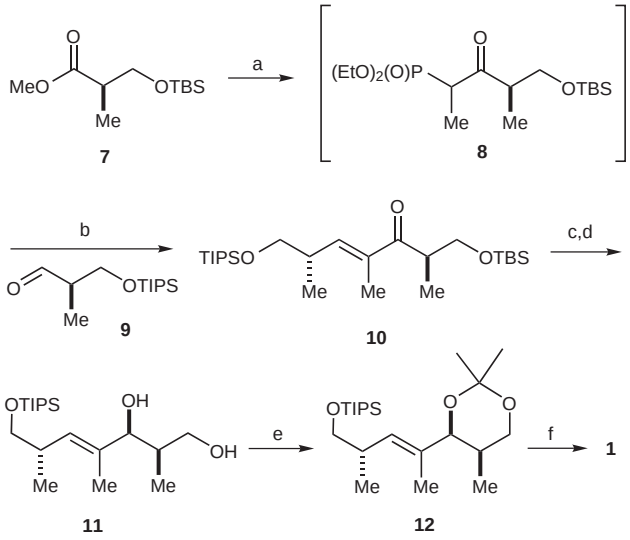


Figure 2

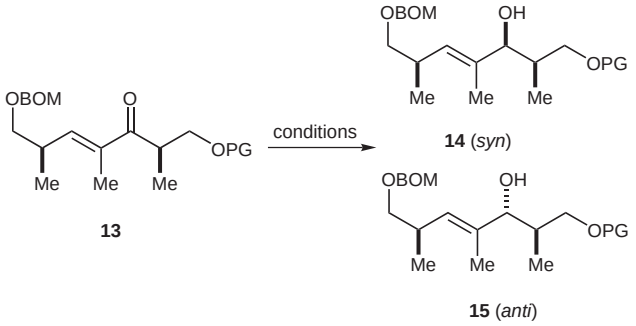


Scheme 3 *Reagents and conditions*: a) diethylethanephosphonate, LDA, Et_2O, –78 °C, 30 min, 80%; b) i. $Ba(OH)_2$, THF–water (v/v 40:1), 22 °C, 30 min; ii. **9**, 0 °C, 7 h, 65%; c) HF–pyridine, THF, 0 °C, 45 min, 79%; d) $Zn(BH_4)_2$, Et_2O, 0 °C, 45 min, 90%; e) 2,2-dimethoxypropane, camphorsulfonic acid, CH_2Cl_2, 60 min, 22 °C, 99%; f) i. BH_3·DMS, THF, 22 °C, 60 min; ii. NaOH, 30% H_2O_2, 0 °C, 90 min, 64%

Encouraged by this result we used enones **13** and **16** in a systematic model study on the stereoselectivity of the carbonyl reduction (Table 1 and Table 2).

Clearly, the *syn*-alcohols **14** and **17** are the result of a chelate Cram mechanism, whereas the *anti*-diastereomers **15** and **18** result from a Felkin–Anh attack (Figure 3). The data collected in Table 1 and Table 2 show how the protective group at the C-1-OH and the reagent bear on the stereochemical outcome of the reaction. The TBS-protected enone **13** shows increasing chelate Cram selectivity

Table 1 Carbonyl Reduction of Enones **13**



13	PG	Conditions	Ratio **14**:**15**	Yield (%)
a	TBS	$Zn(BH_4)_2$, Et_2O	1.4:1	78
		$NaBH_4$, EtOH	1.5:1	83
		N-Selectride, THF	2.7:1	95
		L-Selectride, THF	6.1:1	86
		LAH, Et_2O	9.0:1	79
b	TIPS	LAH, N-Selectride, THF	1.0:1	40
c	Tr	LAH, Et_2O	1:5.0	81
		N-Selectride	1:5.2	95

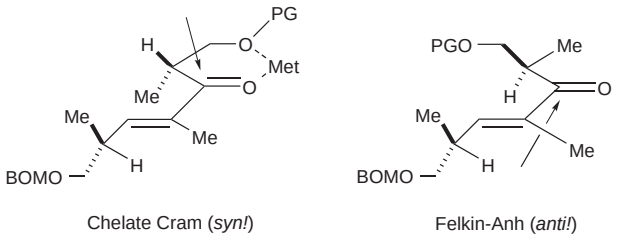
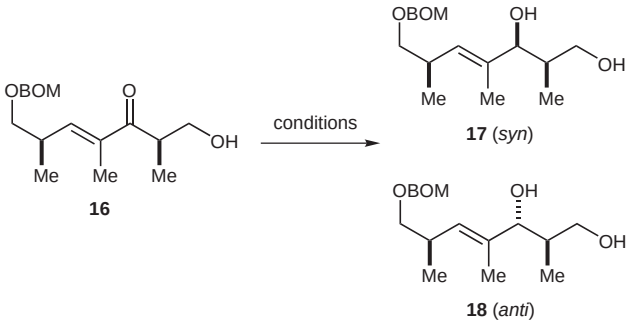


Figure 3

with L-selectride, and lithium aluminium hydride, whereas bulky protecting groups such as TIPS or Tr lead to significant Felkin–Anh preference. The free alcohol induces the chelate Cram mechanism and, under appropriate conditions gives the *syn*-product exclusively (Table 2). A similarly detailed study on the hydroboration[6] (Scheme 4, Scheme 5) revealed that the 3,5-*anti*-diols **20**, **28**, **31** and **34** are formed with high selectivity from **19** and the 1,3-acetonides **12**, **30** and **33**. The remaining olefins form the 3,5-*anti*-products with much lower selectivity. Thus, all the olefins are attacked by the borane from the *si*-*si*-face. This result excludes internal delivery processes, because in this case the selectivity should strongly depend on the configuration the C-3-OH. Therefore we suggest that free alcohols **19**, **14c** and **15a**, with the first equivalent of diborane, form a boronate, which is then further attacked at the double bond by a second diborane molecule. The stereochemical outcome may be rationalized on the basis of conformational studies of the starting materials. For

Table 2 Carbonyl Reduction of Enone **16**

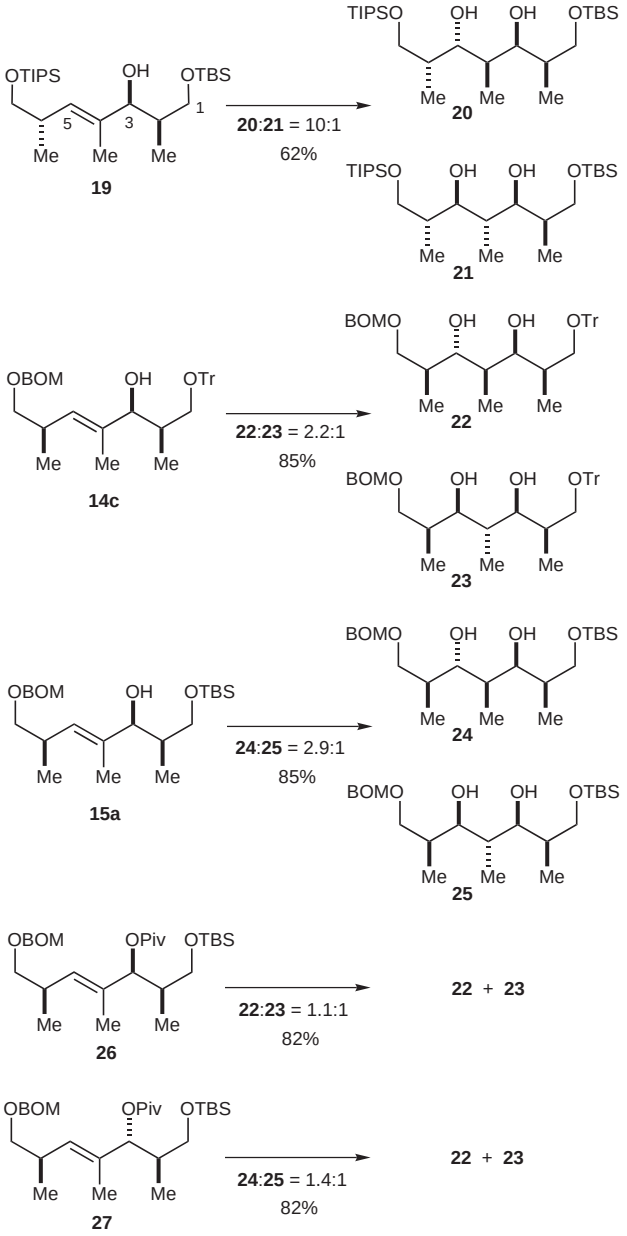


Conditions	Ratio **17**:**18**	Yield (%)
L-Selectride, THF	3.5:1	91
$NaBH_4$, EtOH	4.6:1	95
LAH, Et_2O	7.0:1	95
DIBALH, THF	22:1	74
$Zn(BH_4)_2$, Et_2O	47:1	93
$Me_4NBN(OAc)_3$	>99:1	84
BH_3, THF	>99:1	94

instance the crystal stucture of alcohol **14c** (Figure 4) may serve as a model for the acyclic alcohol derivatives. It shows a sickle like conformation which is the result of $A^{1,3}$-strain[7] between the C-4-methyl group and the stereogenic centers at C-2 and C-6, respectively. This effect places one substituent on each center on top of the 4,5-olefin plane; in **14c** these residues are 6-methyl and 3-OBRR′, which hinder the attack from the top face and direct the borane to the bottom face (*si*-*si*-face) with low selectivity. If, however, as in **19**, both positions are occupied by bulky residues (OBRR′ and CH_2OTIPS), the facial preference for the *si*-*si*-face was quite high. The acetonides **12** and **33** were studied by ^1H NMR ROESY experiments, which revealed ground state conformations in which due to $A^{1,3}$-strain effects the olefin side chain adopts a skew conformation with respect to the acetonide (Figure 5 and Figure 6). The *re*-*re*-face of the olefin is shielded by the acetonide ring. The configurations of the stereogenic centers at C-2 and C-6 have no influence on the stereochemical course.

As a further synthetic application, fragment *ent*-**14c** nicely matches the C-5-C-11-part of the ansamycin macbecin I (Figure 7).[8]

A more extensive application of the HWE methodology is aiming for a total synthesis of the polyol antibiotic zincophorin.[9] Our retrosynthetic analysis envisaged the construction of the carbon skeleton from the fragments **36**, **37** and **4**, which should be connected by a HWE olefination between C-9 and C-10 and a Julia–Lythgoe olefination between a C-16 aldehyde and a C-17-sulfone (Scheme 6).



Scheme 4 Stereocontrol of the hydroboration of acyclic olefins **19**, **14c**, **15a**, **26** and **27**

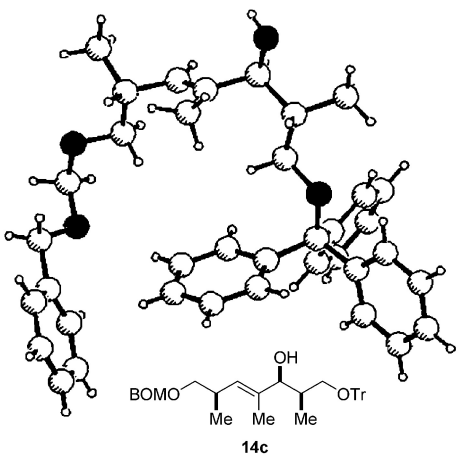
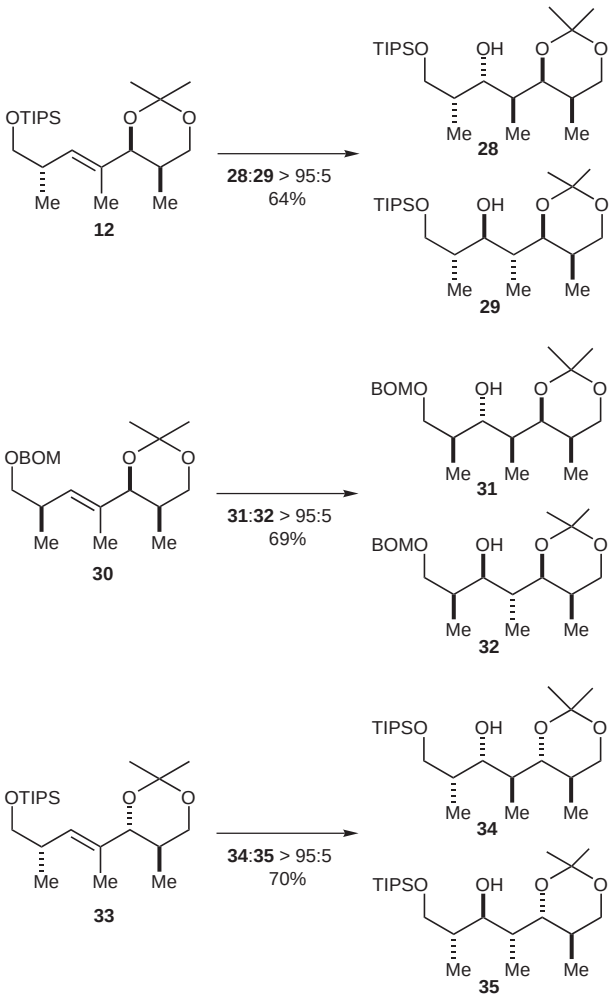


Figure 4 Crystal structure of **14c**



Scheme 5 Diastereomeric ratio for the hydroboration of acetonides **12**, **30** and **33**

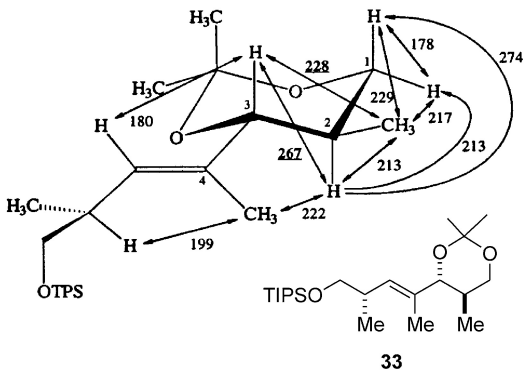


Figure 5 ROESY analysis of **33** (atom distances in pm)

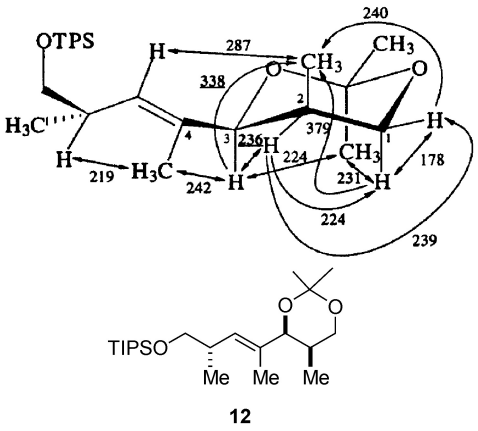


Figure 6 ROESY analysis of **12** (atom distances in pm)

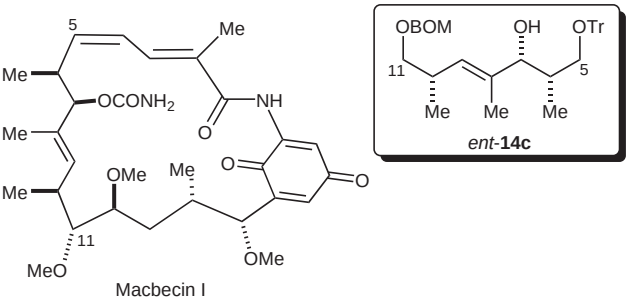
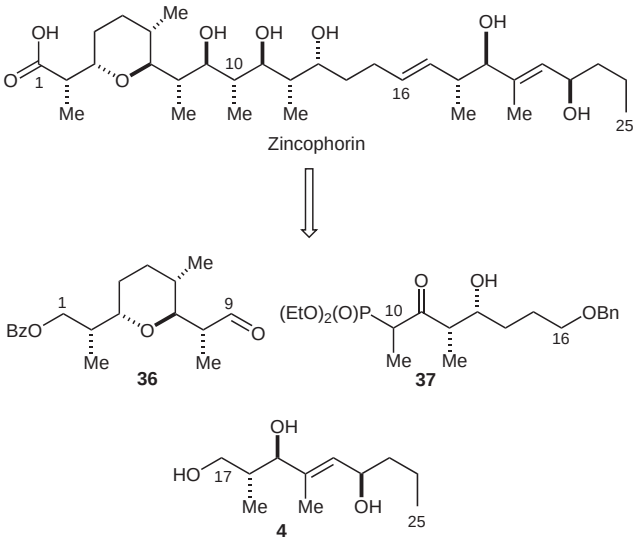


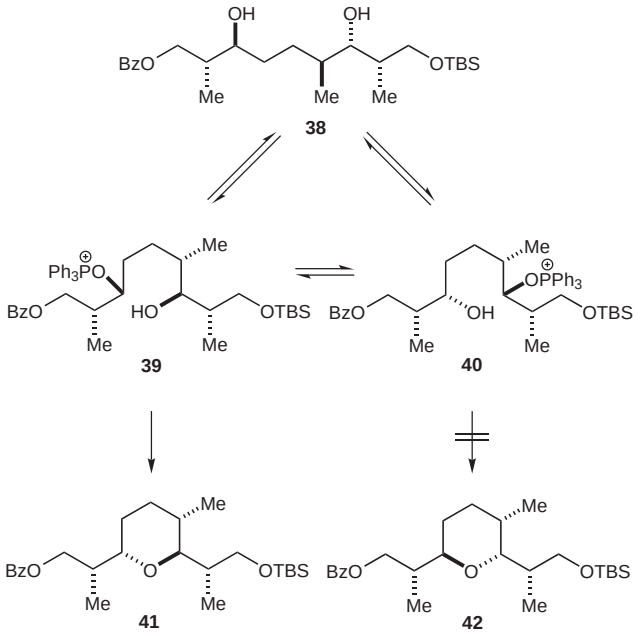
Figure 7



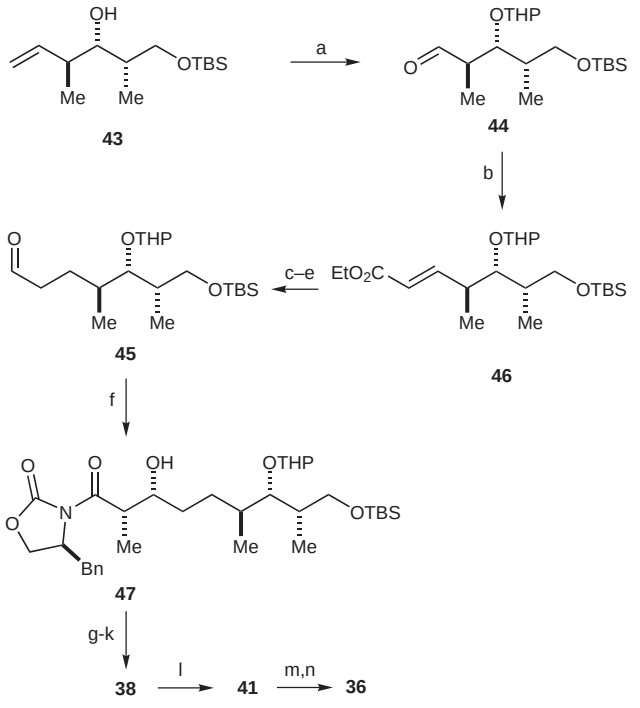
Scheme 6

The synthesis of the tetrahydropyran fragment **36** was centered around a Mitsunobu cyclization[10] of diol **38**, which, in principle could give either **41** or its diastereomer **42**, depending on whether activated intermediate **39** or **40** was formed preferentially (Scheme 7). Thus, **38** was prepared from known precursor[11] **43** in good overall yield and stereocontrol along the route shown in Scheme 8.

Stereotriad **43** was transformed into into aldehyde **44** which was subjected to an Evans aldol addition[12] to furnish adduct **45** with high stereoselectivity. Removal of the auxiliary and of the THP protecting group led to diol **38**, which under Mitsunobu conditions cyclized to tetrahydropyran **41** exclusively. This result indicated that the path via **39** was the favored one, which means that the bulky phosphonium group was attached to the less hindered C-



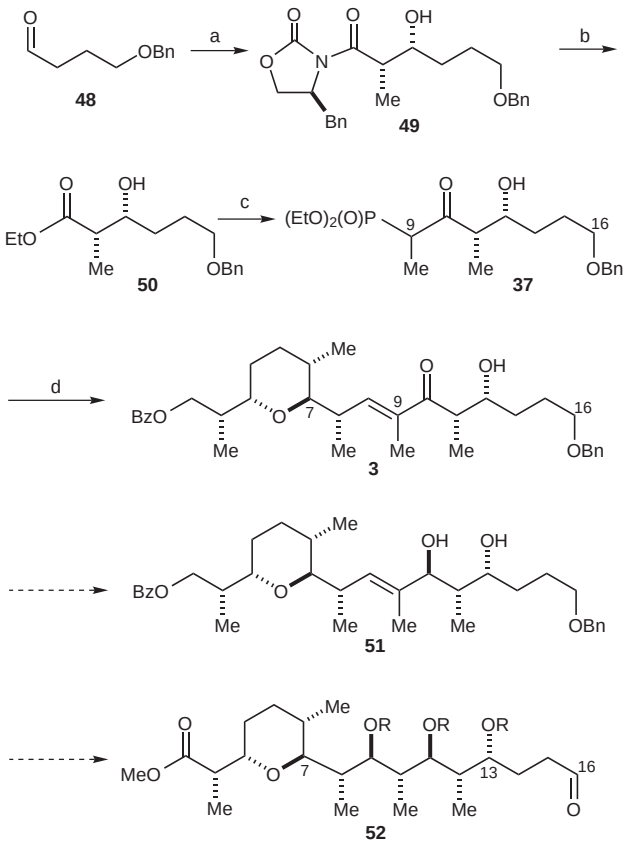
Scheme 7



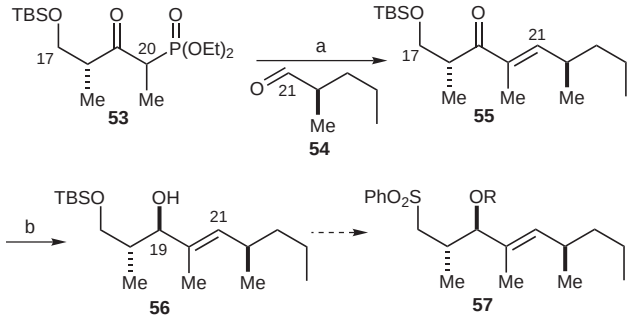
Scheme 8 *Reagents and conditions*: a) DHP, CH_2Cl_2, PPTS, 22 °C, 40 h, 89%; b) i. ozone, MeOH, –78 °C; ii. TPP, 22 °C, 16 h; iii. diethylmethanephosphonate, NaH, THF, –15 °C, 1 h; iv. **44**, THF, 0–22 °C, 3 h, 92%; c) EtOH, Raney-nickel, H_2, 1 bar, 22 °C, 5 h, 99%; d) DIBALH (1.2 M in toluene), THF, –70 °C to 0 °C, 2 h, 99%; e) oxalylchloride, DMSO, N*i*-PrEt_2, CH_2Cl_2, –78 °C to 50 °C, 20 min, 95%; f) (4*R*)-*N*-propionyl-4-benzyl-oxazolidinone, dibutylborontriflate, Et_3N, CH_2Cl_2, –65 °C, 90 min, 97%; g) i. tributylborane, propionic acid, THF, 22 °C, 90 min; ii. lithiumborohydride (1 M in THF), 0–22 °C, 14 h, 89%; h) benzoylchloride, pyridine, –15 °C to 22 °C, 3 h, 88%; k) Me_2AlCl (1 M in hexane), CH_2Cl_2, –25 °C, 2 h, 88%; l) TPP, DEAD, toluene, 22 °C, 16 h, 56%; m) PPTS, MeOH, 22 °C, 16 h, 95%; n) see e), 95%

3-alcohol function and the more hindered C-7-hydroxyl group acted as the nucleophile. Desilylation and oxidation furnished aldehyde **36**. Separately, phosphonate **37** was prepared from the known aldehyde **48**[13] as shown in Scheme 9, and connected with **36** to form the enone **3**. Evans–Carreira reduction[14] should generate *anti*-diol **51**, however, the ensuing hydroboration, which underlies doubly stereodifferentiating influences from both sides, has yet to be performed. In the end aldehyde **52** should be generated. The missing C-17-C-25-fragment **56** was prepared as shown in Scheme 10. The carbonyl reduction of **55** to **56** was performed with the CBS reagent[15] with 80% de. The exchange of the terminal hydroxyl for a phenylsulfonyl group should generate **57**. With the intermediates **52** and **57** in hands we would intersect Danishefsky's synthesis.[9] Alternatively, the C-7-C-13-segment of zincophorin can readily be prepared in form of acetonide **58** from compound **15c** (Scheme 11).

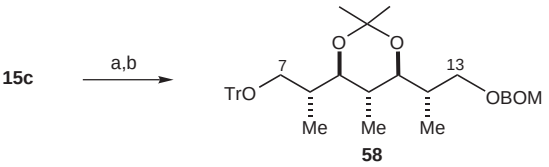
The HWE reduction sequence is also suitable for controlling remote stereogenic centers, as demonstrated in the total synthesis of the macrodiolide antibiotic tartrolon B[16] (Scheme 12). The retrosynthetic disconnection leads to the mono-secoacid precursor **59**, which was assembled via an aldol addition of ketone **60** to aldehyde **61**. Ketone **60** was prepared via the HWE route shown in Scheme 12.



Scheme 9 *Reagents and conditions*: a) (4*R*)-*N*-propionyl-4-benzyl-oxazolidinone, dibutylborontriflate, Et_3N, CH_2Cl_2, –65 °C, 90 min, 94%; b) $Ti(OEt)_4$, EtOH, reflux, 14 h, 95%; c) diethylethanephosphonate, LDA, Et_2O, –78 °C, 30 min; 67%; d) i. $Ba(OH)_2$, THF–water (v/v 40:1), 22 °C, 1 h; ii. **36**, 0 °C, 16 h, 65%



Scheme 10 *Reagents and conditions*: a) i. $Ba(OH)_2$, THF, 22 °C, 1 h; ii. **54**, 0 °C, 16 h, 82%; b) (*S*)-CBS catalyst (0.1 equiv), BH_3·THF (1 M in THF), THF, 0 °C, 10 min, 69%



Scheme 11 *Reagents and conditions*: a) i. BH_3–DMS, THF, 0 °C, 4 h; ii. H_2O_2, NaOH, 22 °C, 90 min, 85%; b) 2,2-dimethoxypropane, camphorsulfonic acid, CH_2Cl_2, 60 min, 22 °C, 98%

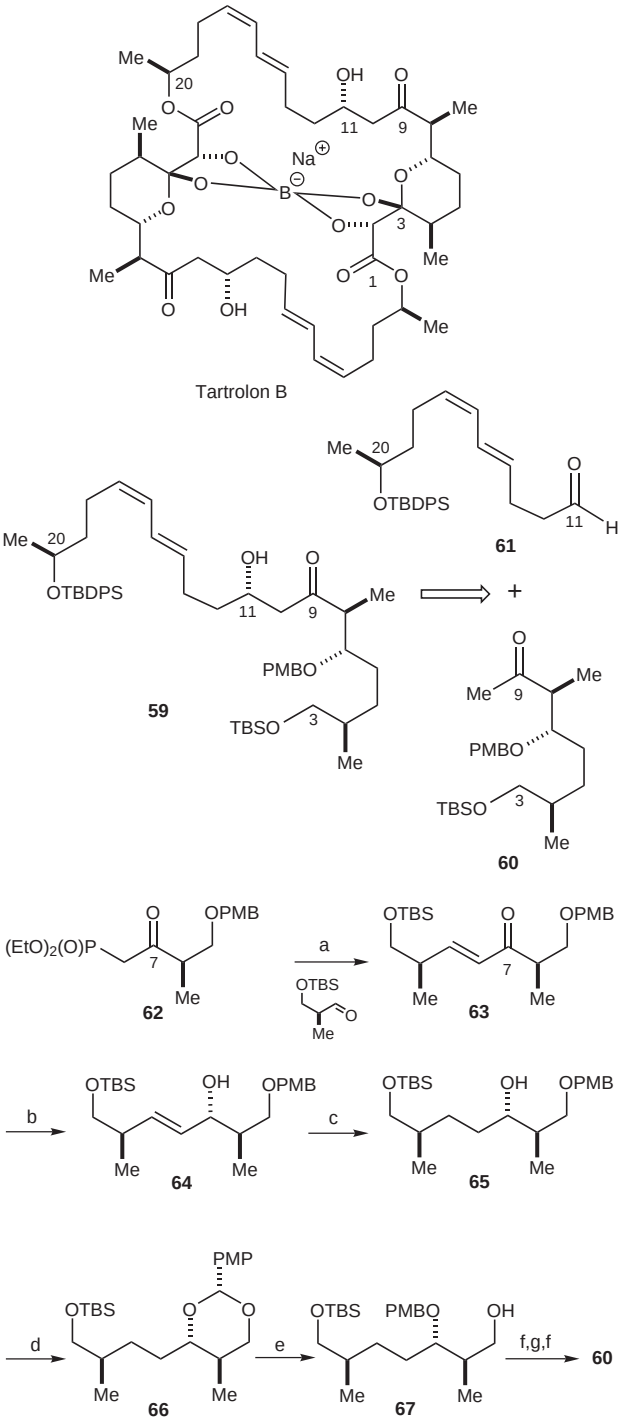
The crucial carbonyl reduction to allylic alcohol **64** was achieved with 10:1 selectivity with the CBS reagent.

To generate monosaccharide polyols HWE reactions with the glyceraldehyde derivatives **69** and **77** were investigated. As shown in Scheme 13 a variety of hydroxylated enone derivatives were obtained *E*-selectively with acceptable yields.

As a specific target the branched pentoses mycarose and arcanose were chosen, which are monosaccharide components in the antibiotics erythromycin D[17] and lankamycin,[18] respectively (Figure 8).

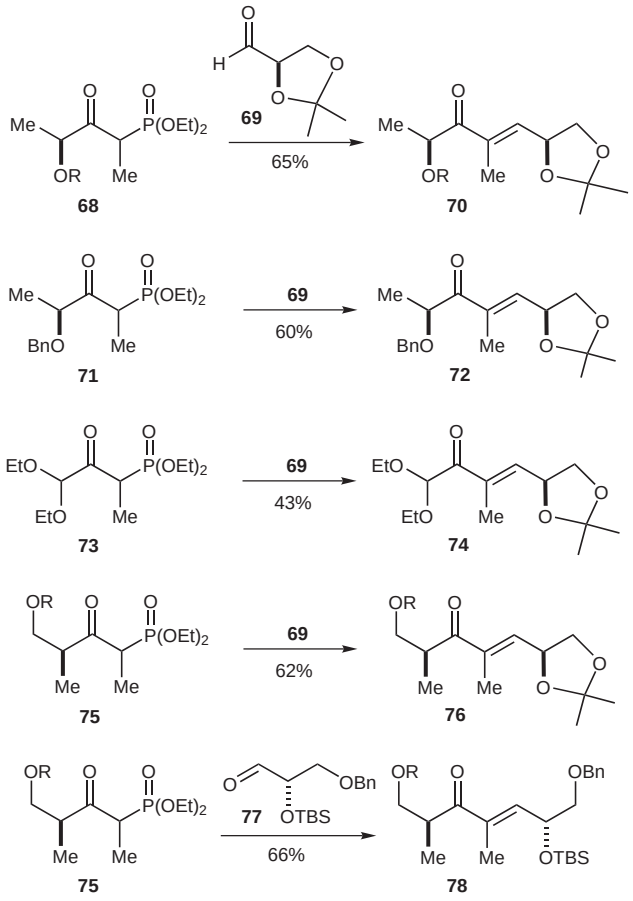
The synthesis of L-methyl-mycaro-pyranoside is described in Scheme 14. Chelate controlled reduction of enone **72** furnished the *anti*-diol derivative **79**, which was MOM protected. Removal of the acetonide and tritylation at the primary position furnished the free alcohol at C-2, which served for a *syn*-directed epoxidation to give **80**. Reductive epoxide opening at the less hindered position led to **81**, which on glycol cleavage and treatment with methanol and acid gave the pyranose as an anomeric mixture **82**, which was separated by HPLC. The analytical data of the β-anomer were in good agreement with those reported in the literature.[19]

The synthesis of the corresponding arcanosyl derivative (Scheme 15) started with the Felkin–Anh selective reduction of **70** to the *syn*-diol derivative **83**, which was *syn* epoxidized to **84**. Degradation of the acetonide to the aldehyde **85** and reductive opening of the epoxy-aldehyde with zinc led to hydroxy aldehyde **86**, which was converted into ketal **87** with ethylene glycol. O-Methylation with methyltriflate and treatment with methanol and acid gave pyranoside **89** as an anomeric mixture, from which the

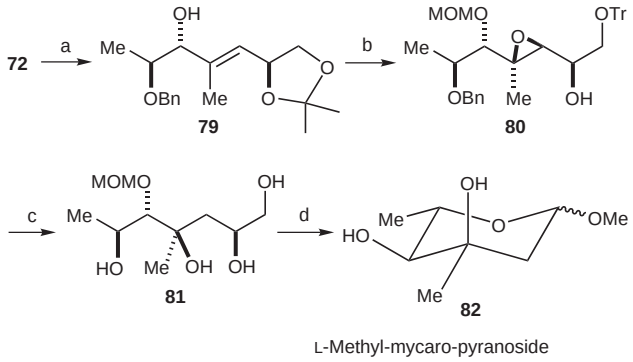


Scheme 12 *Reagents and conditions*: a) i. LiOH, THF–H_2O (40:1), 22 °C, 1 h; ii. aldehyde, 0 °C, 16 h, 90%; b) (*S*)-CBS catalyst (0.1 equiv), BH_3·THF (1 M in THF), THF, 0 °C, 10 min, 84%; c) hydrazine hydrate, O_2, $Cu(OAc)_2$, 95%; d) DDQ, MS 4 Å, CH_2Cl_2, 76%, e) DIBALH, CH_2Cl_2, 40 °C to –10 °C, 91%; f) oxalylchloride, DMSO, N*i*-$PrEt_2$, CH_2Cl_2, –78 °C to 50 °C, 20 min, 92%; g) i. MeMgBr, Et_2O; ii. see f), 83%

β-anomer was isolated by HPLC in pure form. As mentioned above, free arcanose is not a natural product, and the only characterization of the methyl pyranoside is its combustion analysis.[18] The absolute and relative configuration of arcanose, which, to our knowledge, has never

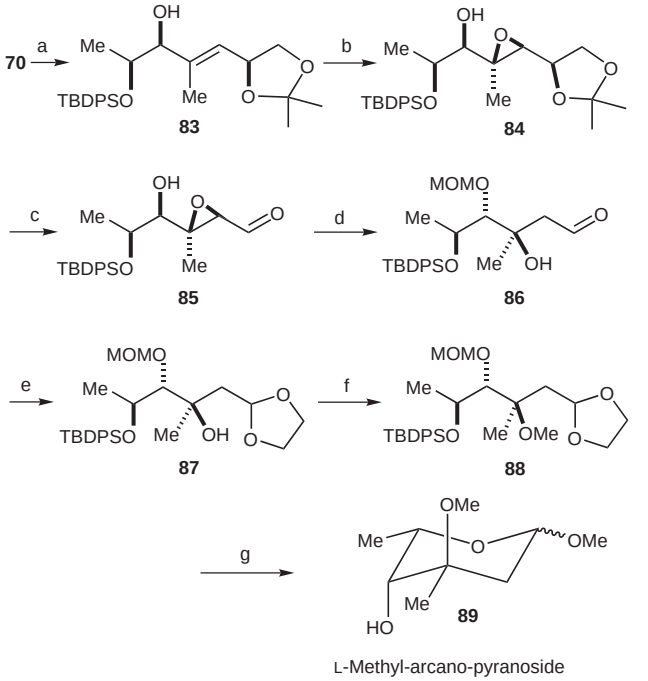


Scheme 13 HWE olefination of aldehydes **69** and **77** (R = TBDPS)



Scheme 14 *Reagents and conditios*: a) $LiAlH_4$ (0.67 M in THF), THF, –20 °C, 2 h, 83% (selectivity 6:1); b) i. MOMCl, CH_2Cl_2, 0 °C, 48 h, 93%; ii. formic acid, MeOH–H_2O (2:1), 22 °C, 2 d, 95%; iii. TrCl, CH_2Cl_2, Et_3N, DMAP, 22 °C, 16 h, 84%; iv. *m*CPBA, CH_2Cl_2, phosphate buffer, 0–22 °C, 2 h, 95%; c) i. $LiAlH_4$ (0.67 M in THF), Et_2O, reflux, 14 h, 60%; ii. Na, NH_3, Et_2O, –78 °C, 15 min, 82%; d) i. PTS, MeOH–H_2O (3:1), THF, 22 °C, 3 d, 99%; ii. $Pd(OAc)_4$, CH_2Cl_2, 22 °C, 30 min; iii. acetylchloride, MeOH, 22 °C, 90 min, 81% (anomeric ratio β:α = 3:1)

been synthesized before, was secured by conversion into its 4-epimer cladinose.[20] The ^1H NMR, ^{13}C NMR, and MS data of our synthetic sample are in full agreement with structure **89**.



Scheme 15 *Reagents and conditions*: a) $MgBr_2{\cdot}OEt_2$, THF, $Zn(BH_4)_2$ (0.6 M in THF), –18 °C, 75 min, 77% (selectivity 11:1); b) *m*CPBA, CH_2Cl_2, phosphate buffer, 0–22 °C, 2 h, 98%; c) i. *p*-TsOH, MeOH–H_2O (3:1), THF, 22 °C, 3 d, 99%; ii. $Pd(OAc)_4$, CH_2Cl_2, 22 °C, 30 min; d) Al-Hg, THF, H_2O, 16 °C, 3d, 72%; e) oxalic acid, MeCN–ethyleneglycol (4:1), 22 °C, 4 h, 72%; f) BuLi (1.6 M in hexane), THF, MeOTf, –50 °C, 4 h, 95%; g) i. TBAF (1 M in THF), THF, 22 °C, 6 d, 92%; ii. *p*-TsOH, MeOH–water (3:1), THF, 22 °C, 3 d, 84%, anomeric ratio β:α = 2:1

In conclusion, we have shown that the HWE olefination in combination with stereo- and regiocontrolled modifications of the enone intermediate is an efficient method for preparing polypropionate and monosaccharide fragments. In this way the HWE methodology may be a welcome supplement to the established aldol strategy.[12] Additional potential of the HWE approach, however, lies in stereocontrolled additions to the double bond or in sigmatropic rearrangements of the corresponding allylic alcohol. These possibilities are currently considered for natural product syntheses in our laboratory.

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References

(1) See for example: Mann, J. *Secondary Metabolism*, 2nd ed.; Oxford Science Publications, Clarenden Press: Oxford, **1995**.
(2) Kelley, S. In *Comprehensive Organic Synthesis*, Vol. 1; Trost, B. M.; Fleming, I.; Schreiber, S. L., Eds.; Pergamon Press: Oxford, **1991**, 761–777.
(3) Mulzer, J.; Martin, H. J.; List, B. *Tetrahedron Lett.* **1996**, *37*, 9177.
(4) Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. K. *J. Am. Chem. Soc.* **1967**, *89*, 5737.

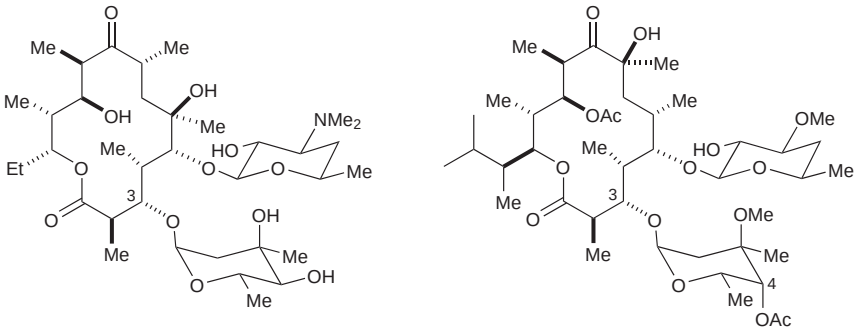

Figure 8

(5) Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1975**, *16*, 4147.
(6) Confer: (a) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. (b) Fukuyama, T.; Wang, C. L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260. (c) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C. L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262.
(7) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(8) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471.
(9) (a) Isolation: Gräfe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 836. (b) See also: Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501. (c) Total syntheses: Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. (d) See further: Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626. (e) Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4341; *Angew. Chem.* **2004**, *116*, 4441.
(10) Mitsunobu, O. *Synthesis* **1981**, 1.
(11) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(12) Braun, M. *Stereoselective Synthesis*, In *Houben–Weyl, Methods of Organic Synthesis*, Vol. E 21b; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1995**, 1644–1656.
(13) Paul, R.; Tschetichoff, S. *Bull. Soc. Chim. Fr.* **1948**, 197.
(14) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(15) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; *Angew. Chem.* **1998**, *110*, 2092.
(16) (a) Schummer, D.; Irschik, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1994**, 283. (b) Total synthesis: Mulzer, J.; Berger, M. *J. Org. Chem.* **2004**, *69*, 891.
(17) Corcoran, J. W.; Chick, M. In *Biosynthesis of Antibiotics*; Snell, J. F., Ed.; Academic Press: New York, **1966**.
(18) Keller-Schierlein, W.; Roncari, G. *Helv. Chim. Acta* **1962**, *45*, 138.
(19) Total syntheses of optically active mycarose: (a) Korte, F.; Claussen, U.; Göhring, K. *Tetrahedron* **1962**, *18*, 1257. (b) Lemal, D. M.; Pacht, P. D.; Woodward, R. B. *Tetrahedron* **1962**, *18*, 1275. (c) Tatsuta, K.; Mukayama, S.; Toshima, K.; Yoshida, T. *Carbohydr. Res.* **1991**, *222*, 173. (d) Flaherty, B.; Overend, W. G.; Williams, N. R. *J. Chem. Soc. C* **1966**, 398. (e) Koft, E.; Dorff, P.; Kullnig, R. *J. Org. Chem.* **1989**, *54*, 2936.
(20) Keller-Schierlein, W.; Roncari, G. *Helv. Chim. Acta* **1966**, *49*, 705.