High Stereochemical Diversity and Applications for the Synthesis of Marine Natural Products: A Library of Carbohydrate Mimics and Polyketide Segments

Andrea M. Misske[a, b] and H. Martin R. Hoffmann*[a]

Abstract: We have developed a powerful concept for the rapid assembly of a series of twenty-four homochiral building blocks from simple racemic *trans*-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one. The series comprises eight stereochemical pentades of anomeric [3.3.1]lactone acetals, eight stereochemical tetrades of anomeric carbohydrate mimics, and eight stereotetrades of acyclic polypropionate units. The utility of these enantiopure materials (average 94 % *ee*) in natural product synthesis is demonstrated and shown to complement the popular aldol method.

Keywords: aldol reactions · biodiversity · carbohydrate · combinatorial chemistry · polyketides

Introduction

In general, the formation of a racemic mixture in a classical total synthesis is undesirable and a considerable drawback indicating lack of stereocontrol and necessitating separation of the enantiomers by additional steps with loss of one half of material. Another path to enantiomerically pure compounds employs the chiral pool[1] which although often very effective, is of limited scope since the choice of absolute configuration is generally limited by the configuration of natural enantiomer.

Developing the concept of the "*early racemic switch*" we have deliberately avoided using enantiomerically pure starting material.[2, 3] Instead the racemic mixture is regarded as two key single isomers which are elaborated simultaneously to structurally different bioactive natural products in a modified mix-and-split combinatorial strategy. The first steps involve the selected racemic material. In further steps reaction paths involving several sites are generated thanks to the presence of pro-stereogenic sp^2 centers. Finally individual building blocks are formed. These are easily separated and isolated. As both enantiomers are used from the beginning, there is no loss of material. Moreover, fewer steps have to be carried out overall (Scheme 1).

Using this general approach we have previously reported the synthesis of two seven carbon segments of (−)-discodermolide and phorboxazole A and B.[3] Starting from the racemic oxabicyclic system with *anti*-2,4-dimethyl groups **1** and ***ent*-1**, we generated the two diastereomeric monocyclic tetrahydropyran units **15** and **18** (Scheme 2). Disregarding the anomeric center which is removed at a later stage both **15** and **18** contain four stereocenters. They were prepared in high enantiomeric purity and are cyclic polyketide equivalents.

Currently, the most important approach to polyketides is through a directed aldol reaction and auxiliary control involving chiral enolates.[4]

We now describe a modular polyketide synthesis of all $2^3 = 8$ oxabicyclic, monocyclic, and acyclic systems with *anti*-2,4-dimethyl groups that is 24 building blocks altogether. The 2^3 systems with *syn*-2,4-dimethyl groups should be available through desymmetrization of *meso*-compounds using similar chemistry. The general advantage of our approach is outlined in Scheme 3. The popular symmetry-breaking of *meso* compounds requires two *diastereomeric* compounds with *syn*-dimethyl groups (equatorial, equatorial, and axial, axial) as precursors and separate desymmetrization of the two σ-symmetric molecules. The present approach allows us to begin with the simple racemic starting material **1** and *ent*-**1** as two distinct compounds in one flask, reducing number of steps, cutting waste and gaining time.

The artificial chiral pool—A library of polyketide fragments and carbohydrate mimics: Reduction of the racemic [3.2.1]oxabicyclic ketone **1** and ***ent*-1**[3] with either DIBAH or SmI_2[5] provides the axial (89 %) and equatorial alcohol (85 %), respectively, each as a racemic mixture (Scheme 1). Reduction with SmI_2 gives access to the series of *syn*-diol equivalents, reduction with DIBAH to the series of *anti*-diol equivalents (cf. Scheme 2). After protection as a benzyl ether (95 %/99 %) under standard conditions a second *bifurcation* is

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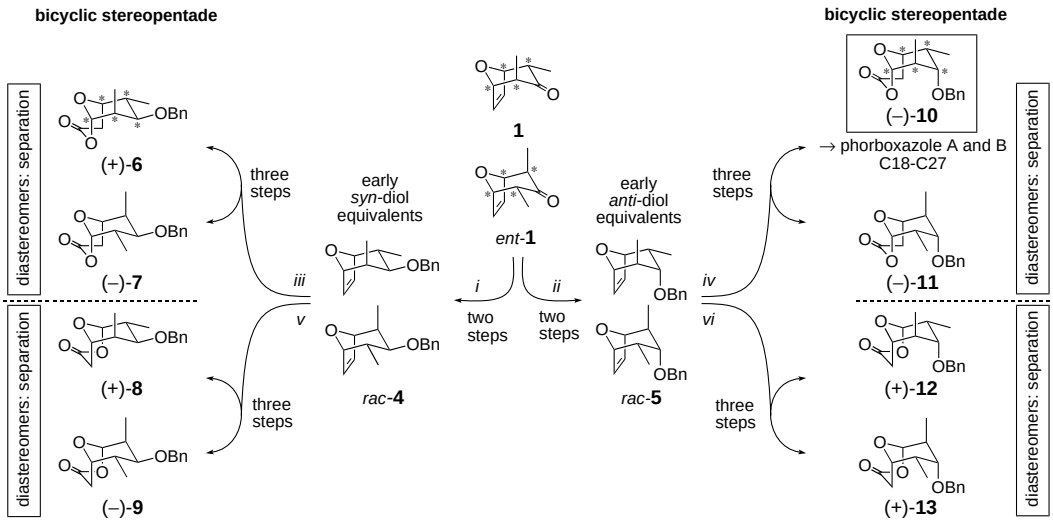
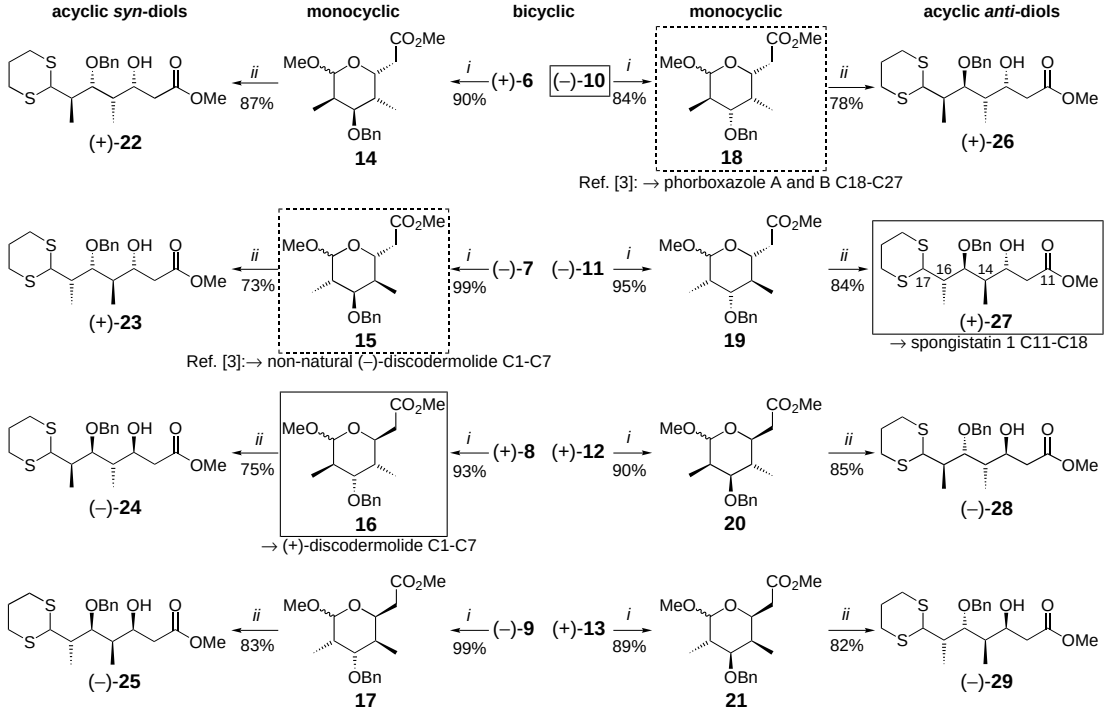


Scheme 1. One racemic ketone *rac*-**1** is transformed into eight separable lactone acetals by cooperative substrate and reagent control. i) 1. SmI_2, isopropanol, THF, reflux, 2 h, 85%; 2. NaH, THF, BnBr, reflux, 15 h, 95%; ii) 1. DIBAH, THF, −78 °C, 11 h, 89%; 2. NaH, THF, BnBr, reflux, 16 h, 99%; iii) 1. (−)-$(Ipc)_2BH$, THF, −25 → −10 °C, 7 d, then NaOH, H_2O_2, 2 h, 83%; 2. PCC, 4 Å MS, NaOAc, CH_2Cl_2, rt, 1.5 h, 97%; 3. *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 15 h, 83% (**6**: 39%, *ee* = 96%; **7**: 44%, *ee* = 89%); iv) 1. (−)-$(Ipc)_2BH$, THF, −15 °C, 14 d, then NaOH, H_2O_2, 3 h, 98%; 2. PCC/SiO_2, CH_2Cl_2, rt, 15 h, 96%; 3. *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 15 h, 85% (**10**: 47%, *ee* > 95%; **11**: 38%, *ee* = 93%); v) 1. (+)-$(Ipc)_2BH$, THF, −25 → −10 °C, 7 d, then NaOH, H_2O_2, 2 h, 87%; 2. PCC, 4 Å MS, NaOAc, CH_2Cl_2, rt, 1.5 h, 98%; 3. *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 15 h, 83% (**8**: 47%, *ee* = 91%; **9**: 40%, *ee* = 94%); vi) 1. (+)-$(Ipc)_2BH$, THF, −25 → −10 °C, 7 d, then NaOH, H_2O_2, 2 h, 82%; 2. PCC, 4 Å MS, NaOAc, CH_2Cl_2, rt, 1.5 h, 99%; 3. *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 15 h, 82% (**12**: 37%, *ee* = 95%; **13**: 45%, *ee* = 96%). DIBAH: Diisobutylaluminum hydride, Ipc: isopinocampheyl, PCC: pyridinium chlorochromate, *m*-CPBA: *meta*-chloroperoxybenzoic acid.



Scheme 2. Further development of synthetic tree (see Scheme 1). Eight anomeric tetrahydropyran esters and eight polypropionate stereotetrades: 8+8 = 16. i) MeOH, H_2SO_4, rt, 15 h; ii) 1,3-propanedithiol, TMSOTf, MeCN, −40 → −10 °C, 1 h. TMSOTf: Trimethylsilyl trifluoromethanesulfonate.

introduced doubling the number of stereoisomers from four to eight: Reagent-induced asymmetric hydroboration[6] of the double bond with (−)-$(Ipc)_2BH$ and also (+)-$(Ipc)_2BH$ followed by oxidation with H_2O_2 furnishes a total of four different mixtures of two *diastereomeric* alcohols each (82–98%). Two further oxidations, first with PCC furnish the ketones (96–99%) and then regioselective Baeyer–Villiger oxidative rearrangement (82–85%) gives the series of eight lactone acetals (four pairs of lactones) (+)-**6** and (−)-**7**/(+)-**8** and (−)-**9**/(−)-**10** and (−)-**11**/(+)-**12** and (+)-**13** which at this stage are separated by simple flash chromatography (e.g., silica gel, petrol ether/EtOAc 5:1). At this stage elaborate

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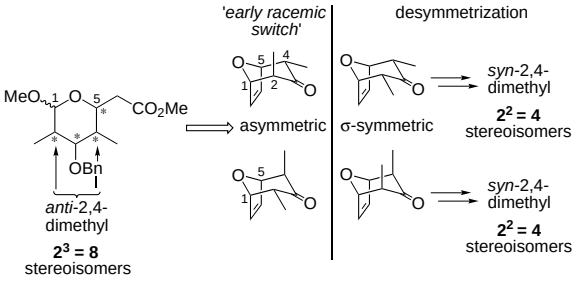


Scheme 3. Strategy for stereochemical diversity from racemic and *meso*-configured substrates.

separation techniques such as HPLC are unnecessary. The resulting anomeric [3.3.1]lactone acetals are versatile synthetic building blocks and are now elaborated separately. Acidic methanolysis gives eight monocyclic acetal esters **14**–**21** (84–99%), each as an anomeric mixture (Scheme 2). A simple further step that is *trans*-thioacetalization with 1,3-propanedithiol and equimolar trimethylsilyl triflate in solvent acetonitrile (the less polar dichloromethane does not allow tetrahydropyran opening) yields eight individual acyclic polyketide segments with a backbone of seven carbon atoms, that is (+)-**22**, (+)-**23**, (−)-**24**, (−)-**25**, (+)-**26**, (+)-**27**, (−)-**28**, and (−)-**29** (73–87%).[7] The enantiomeric excess is very high for all reactions and ranges from 89–96% *ee* (average 94% *ee*).

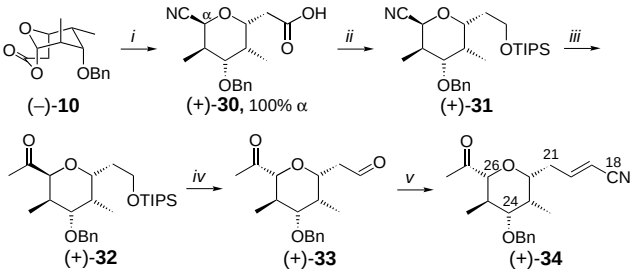
Thus, the artificial chiral pool contains $8 \times 3 = 24$ homochiral building blocks and has been built up in only 32 steps! The sequence from ketone ***rac*-1** as starting material to an acyclic polypropionate unit comprises seven steps. Conventional synthesis of all eight diastereomeric acyclic fragments would require $7 \times 8 = 56$ steps. In fact, our approach to stereochemical diversity saves 24 steps in total. Thus, there results a theoretical number of 16:8 = 2 steps for each [3.3.1]lactone acetal, 24:8 = 3 steps for each anomeric acetal ester and 32:8 = 4 steps for each acyclic polypropionate unit.

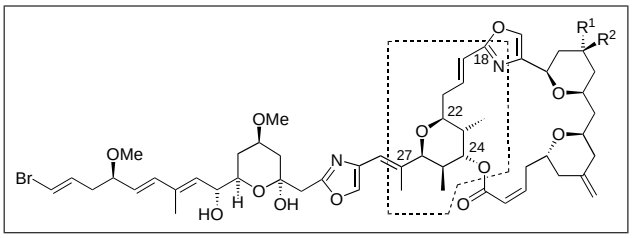
Traditional calculation of the yield of a classical organic synthesis presupposes that half of the racemate is lost and that in the separation step the yield cannot rise above 50%. In our case, both enantiomers of the racemate are used and there is no loss of substance. We consider the enantiomeric pair as two specific starting materials giving different targets in single flask operations. Once several chiral centers are present in a floppy molecular ensemble the separation of diastereomeric mixtures may become troublesome or even impossible. In our case the special array and confrontation of five contiguous stereocenters at the anomeric [3.3.1]lactone stage allows easy separation into single isomers by conventional chromatography. The average yields are 54% ([3.3.1]lactone acetals), 50% (anomeric acetal esters), and 46% (acyclic polypropionate units).

The resulting eight stereochemical pentades (there are eight stereoisomers, since the two stereocenters at the bridgehead cannot be inverted independently) and the 8+8 stereotetrades may be taken as precursors for segments of natural products such as lonomycins A–C,[8] spongistatins,[9] rifamycin S,[10] phorboxazole A and B,[11] (+)-discodermolide,[12] and apoptolidin.[13]

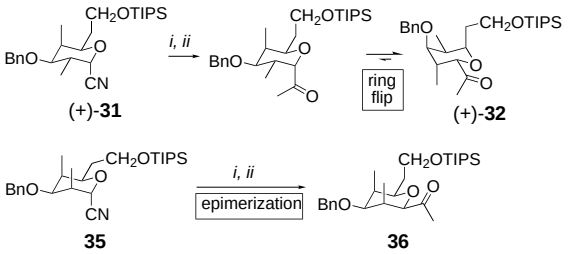
Application to marine metabolite synthesis: To exemplify our approach, we have targeted three segments of prominent polyoxygenated marine natural products i) phorboxazole A and B, ii) (+)-discodermolide and iii) spongistatin 1. Each type of bicyclic, monocyclic, and acyclic building block has been used as starting material, that is [3.3.1]lactone acetal (−)-**10**, monocyclic acetal ester **16**, and acyclic polypropionate building block (+)-**27**, respectively.

i) For the synthesis of the C18–C27 segment of phorboxazole A and B (Scheme 4) a nitrile group was introduced into oxabicyclic [3.3.1]lactone (−)-**10** giving α-anomer (+)-**30** exclusively and in quantitative yield in solvent acetonitrile.[14] Again, the polar solvent acetonitrile and equimolar trimethylsilyl triflate are important for *C*-glycosidation. After reduction of the carboxylic acid to the alcohol (94%) and quantitative protection of the alcohol as TIPS-ether (+)-**31** the nitrile group was converted into methyl ketone (+)-**32** using MeMgBr in toluene, ultrasound and then 0.5 N HCl (76%, 93% based on recovered starting material). After deprotection of the alcohol (97%) the 2,6-*trans*-*C*-glycoside was epimerized to its 2,6-*cis*-epimer with DBU under reflux in 89% yield. Interestingly in model work a carbohydrate mimic epimerized spontaneously when using the methylation protocol (Scheme 5). Conversion of nitrile **35** into the methyl ketone gave the 2,6-*cis*-epimer **36** directly, whereas the methyl ketone from nitrile (+)-**31** undergoes a ring flip and adopts the conformation with equatorial keto function as in (+)-**32** and with *three* rather than two axial substituents.[15]





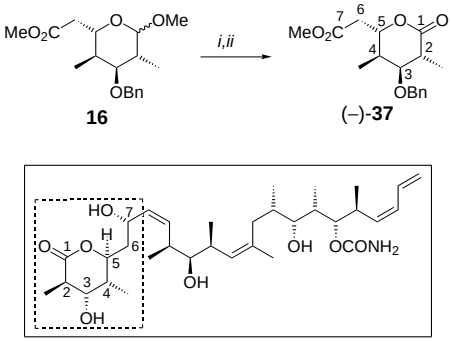
Scheme 4. C18–C27 segment (+)-**34** of phorboxazole A and B. i) TMSCN, TMSOTf, MeCN, −40 → −20 °C, 100%; ii) 1. $BH_3 \cdot THF$, CH_2Cl_2, 0 °C, 3 h, 94%; 2. TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 15 h, 100%; iii) MeMgBr, toluene, rt, ultrasound, 15 h, then 1N HCl, 0.5 h, 76% (93% based on recovered starting material); iv) 1. TBAF, THF, rt, 1 h, 97%; 2. DBU, CH_2Cl_2, reflux, 48 h, 89%, R:S > 40:1; 3. Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 96%; v) Ph_3PCHCN, LiCl, toluene, rt, 15 h, 89%, E:Z > 10:1. TIPSCl: Triisopropylsilyl chloride, TBAF: tetra-*n*-butylammonium fluoride, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 5. Conformational and configurational effects in model cyanoglycosides. i) MeMgBr, toluene, rt, ultrasound; ii) 1N HCl.

Oxidation of the alcohol with Dess–Martin periodinane[16] furnished aldehyde (+)-**33** (96%) which was converted into α,β-unsaturated nitrile (+)-**34** with cyanomethylidene triphenylphosphine[17] in excellent yield and selectivity (89%; $E{:}Z > 10{:}1$). Starting from lactone (−)-**10** the fully resolved central C18–C27 unit of phorboxazole A and B (five stereocenters, one *E*-configured double bond) was obtained in eight steps in 53% yield ($ee > 95\%$).[18]

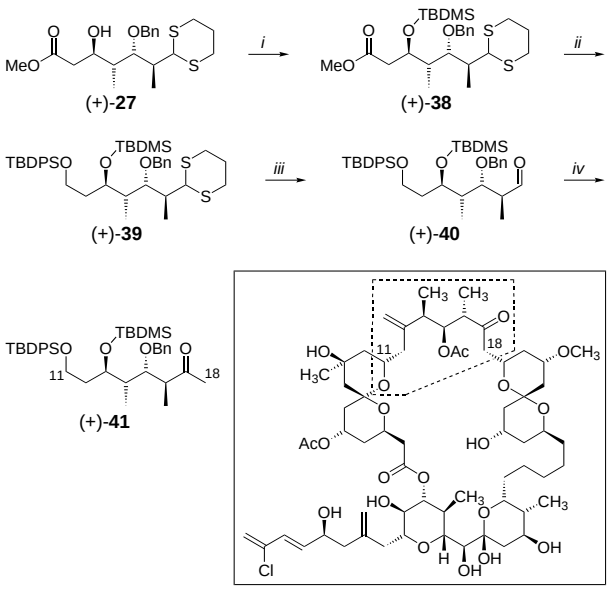
ii) The C1–C7 segment of natural (+)-discodermolide was synthesized in only two steps in 75% and 91% *ee* from anomeric pseudoglycoside **16** (Scheme 6). Acidic hydrolysis in aqueous acetic acid and TPAP/NMO oxidation[19] of the resulting lactol furnished lactone (−)-**37** with four stereocenters.[20]



Scheme 6. C1–C7 segment (−)-**37** of natural (+)-discodermolide: i) H_2O, AcOH, 45–50 °C, 87 h, 80%; ii) TPAP, NMO, 3 Å MS, 6 h, 94%. TPAP: Tetrapropylammonium perruthenate, NMO: *N*-methylmorpholine-*N*-oxide.

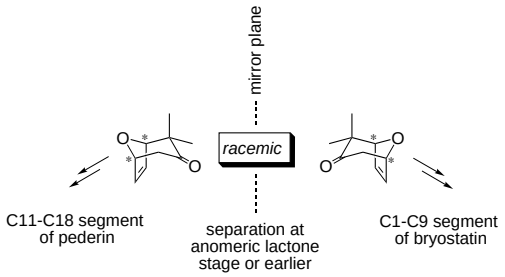
iii) Polyketide unit (+)-**27** was used as starting material for the C11–C18 segment of spongistatin 1 (Scheme 7). After protection of the hydroxyl group as TBDMS ether (+)-**38** in 89% yield the methyl ester was reduced with DIBAH (87%) and the resulting primary alcohol protected as TBDPS ether (+)-**39** (91%). Deprotection of the dithiane unit with $HgCl_2$/HgO furnished the aldehyde (+)-**40** (91%).[21] Reaction with MeMgBr (96%) and PCC oxidation[22] of the secondary alcohol (90%) gave methyl ketone (+)-**41**.

Altogether the C11–C18 segment of spongistatin 1 was synthesized in six steps from polyketide building block (+)-**27** in an overall yield of 55% with an *ee* of 93%.[23]



Scheme 7. C11–C18 Segment (+)-**41** of spongistatin 1: i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 5 h, 89%; ii) 1. DIBAH, THF, 0 °C, 6 h, 87%; 2. TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt, 3 h, 91%; iii) acetone, H_2O, HgO, $HgCl_2$, 60 °C, 3 h, 91%; iv) 1. MeMgBr, THF, rt, 4 h, 96%; 2. PCC, NaOAc, 4 Å MS, 1 h, 90%.

iv) We have already synthesized the C1–C9 segment of bryostatin 1[24] from the α,α-dimethylated oxabicyclic ketone.[24v] Again, the mirror image isomer need not be discarded, but serves as valuable precursor of the natural product pederin (Scheme 8).[25]



Scheme 8. Oxabicyclic ketone with two stereocenters and three prostereogenic sp^2 centers.

v) The α-monomethylated ketone has been elaborated to the C1–C16 segment of lasonolide A[26] (Scheme 9). The mirror image is a precursor of ratjadone,[27] miyakolide,[28] and spongistatin[9] (Scheme 8). Chromatographic separation at an early stage is straightforward, since we are dealing no longer with diastereomers, but constitutional isomers.

vi) Glycosidic tetrahydropyrans **15** and **18** (Scheme 2) have been elaborated to the non-natural C1–C7 discodermolide,[3] and the central phorboxazole segments,[3] respectively.

vii) A variety of carbohydrate mimics are readily accessible, from anomeric lactone acetals, as shown for the transformation (−)-**10** → (+)-**30**. Furthermore, various monocyclic methyl acetals, here exemplified by eight stereochemical tetrades **14** → **21**, serve as precursors of *C*-glycosidic tetrahydropyrans.[14, 29]

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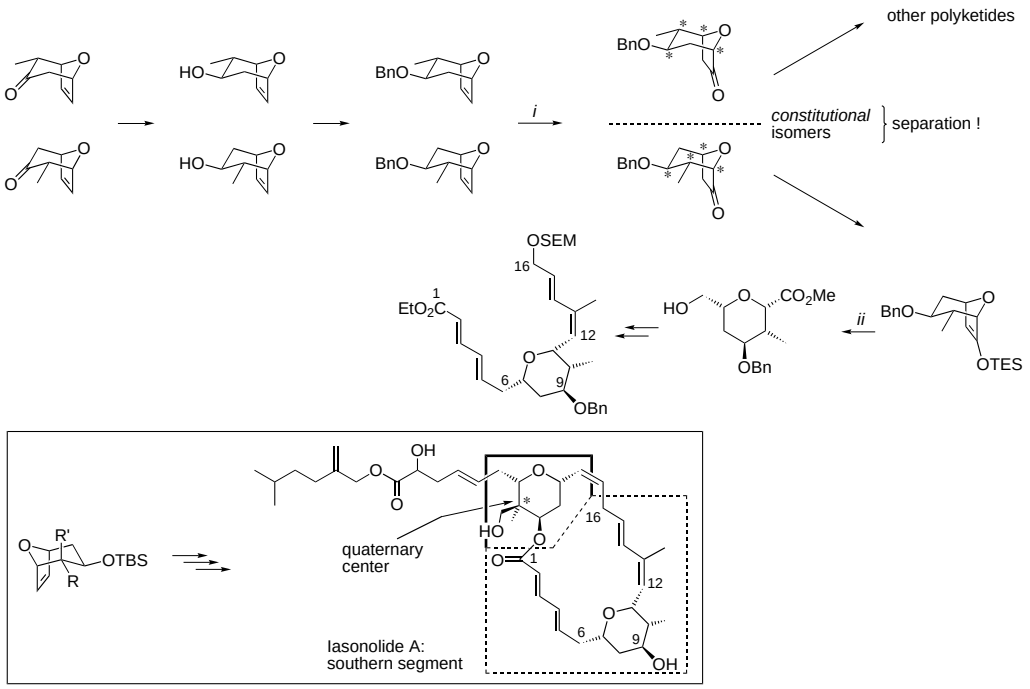

Scheme 9. Artificial pool with four stereocenters. Separation is feasible *before* potential Baeyer–Villiger ring expansion: Oxidative cleavage of unsaturated 2-carbon bridge "through the middle" yields further enantiopure building blocks. i) 1. $(-)$-$(Ipc)_2BH$, THF, $-15\,^{\circ}C$, 7 d, 90% (*ee* = 90%); 2. PCC, CH_2Cl_2, rt, 16 h, 45+45%; ii) 1. O_3, CH_2Cl_2, MeOH, $-78\,^{\circ}C$; 2. Me_2S, then $-10\,^{\circ}C$; 3. CH_2N_2; 4. $NaBH_4$, $-10\,^{\circ}C \rightarrow$ rt, 1 h, 75%. For the synthesis of the northern segment (partially bold frame) see M. Nowakowski, H. M. R. Hoffmann, *Tetrahedron Lett.* **1997**, *38*, 1001.

Conclusion

We have developed and applied a unified and powerful concept for generating stereochemical diversity which is directly relevant to biodiversity and to polyketide and natural product synthesis in general. Starting from one simple racemic substance a cascade of stereoisomeric high-quality building blocks has been generated. 24 Stereoisomers are available in quantity by robust methodology and are built in a total of only 32 steps. The stereoisomers are individually separable and obtained with an average enantiomeric excess of 94%. The synthetic utility of a bicyclic, a monocyclic, and an acyclic building block has been shown by elaboration into three different segments of various marine natural products with excellent yields. Key stereocontrolled reactions have been carried out by taking advantage of cyclic substrates with three pro-stereogenic sp^2 centers. A chiral auxiliary need not be appended. Various structural and stereopatterns are generated and are equivalent to those of multiple aldol additions. Of the eight different stereopatterns listed in Scheme 2 the framed patterns are currently known as constituents of natural products. The stereopattern of [3.3.1]lactone acetal $(-)$-**10** and its derivatives **18** and $(+)$-**26** has also appeared in enzymic work with various polyketide synthases (PKS).[30] All natural and non-natural polyketide segments prepared by us are of obvious interest for combinatorial synthesis. They also serve together with construction or degradation and spectroscopic studies to identify the relative and absolute stereochemistry of polyketides with unassigned stereocenters. The building blocks are rapidly accessible from very few [3.2.1]oxabicyclic ketones (Schemes 10 and 11). Further progress towards automated procedures and solid-phase methodology is expected.

Acknowledgement

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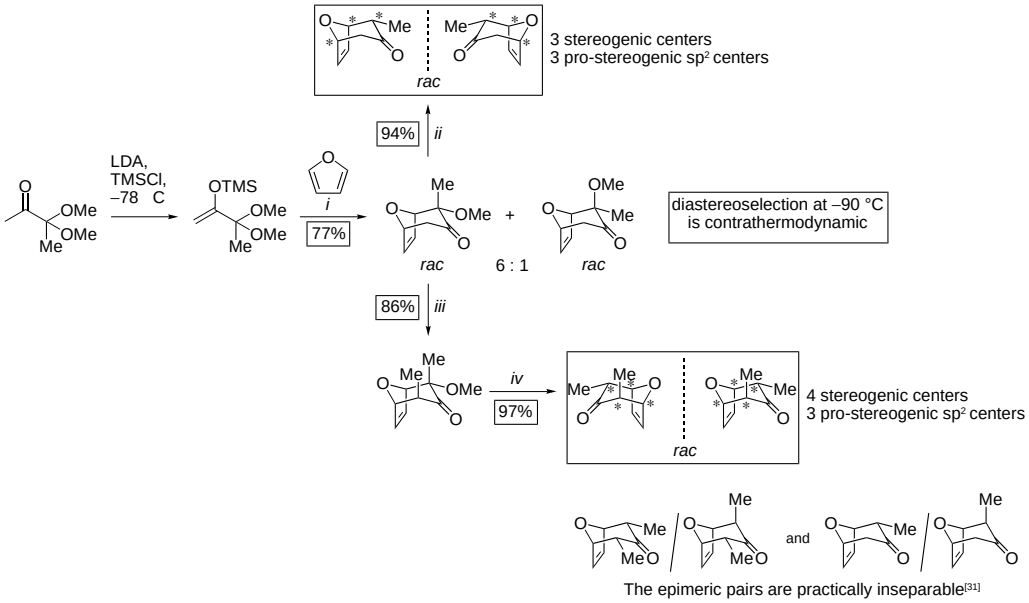
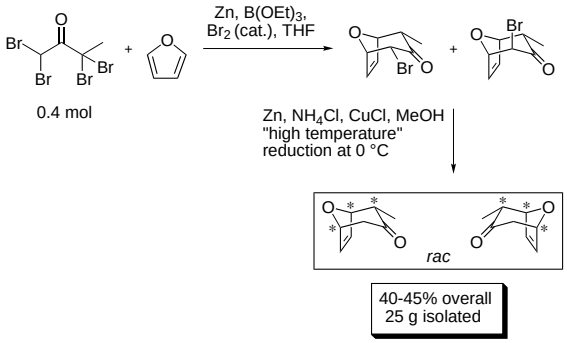


Scheme 10. Synthesis of simple 8-oxabicyclo[3.2.1]oct-6-en-3-ones (cf. Scheme 1): the need to oversynthesize with α-alkoxy (halogen) substituents. i) furan (1 equiv, 68 mmol), TMSOTf (5 mol %, 3.4 mmol), CH_2Cl_2 (150 mL), $-90\,^{\circ}C$; ii) SmI_2, THF, MeOH, $-78\,^{\circ}C \rightarrow$ rt, 16 h, then Zn, reflux, 1 h; iii) LDA, THF, $-78\,^{\circ}C$, TMEDA, MeI, $-78\,^{\circ}C \rightarrow$ rt, 3 h; iv) SmI_2, THF, MeOH, $-78\,^{\circ}C \rightarrow$ rt, then Zn, reflux, 1 h.



Scheme 11. Alternative route to an oxabicycle with an equatorial α-methyl group (cf. Scheme 9 and ref. [5d]).

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