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Preparation and Synthetic Applications of 8-Oxabicyclo[3.2.1]oct-6-en-3-one Derivatives

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Abstract: The development of efficient routes to multi-gram quantities of chiral synthons is a key issue in the total synthesis of natural products and analogues. The conformationally defined and rigid 8-oxabicyclo[3.2.1]oct-6-en-3-one template is an appealing starting material for the development of non-iterative approaches to polyoxygenated fragments that are found in a large variety of biologically relevant natural compounds. Desymmetrization and resolution procedures, stereoselective functionalizations and double-chain elongations represent attractive strategies for such synthetic challenges.

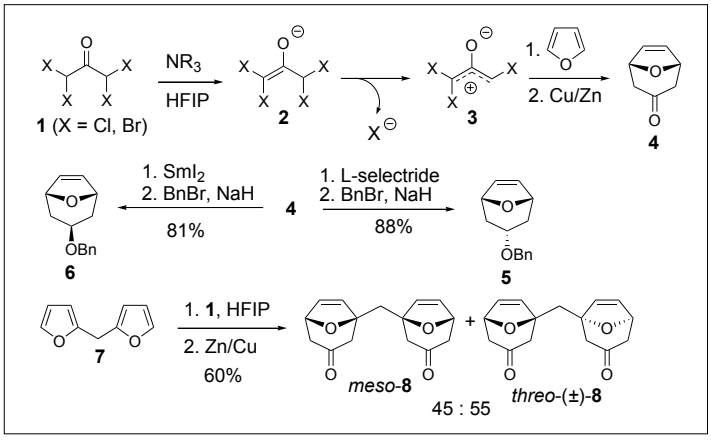
Keywords: [4+3]-Cycloaddition · Furan derivatives · 2-Oxyallyl cations · Polyketides · Two-direction chain elongation

1. Introduction

Polyoxygenated fragments are found in many natural products and constitute attractive targets from a synthetic point of view as well as for their implication in crucial biological pathways. Asymmetric syntheses of these appealing molecules rely on the accessibility of chiral building blocks that can be obtain from the 'chiral pool' or from enantioselective transformations of racemic or achiral starting materials. While iterative methodologies have met with success for the preparation of polyoxygenated skeletons, cycloadditions can offer alternative routes in which many stereocenters can be installed simultaneously on bicyclic adducts. Further stereoselective functionalization of the rigid bicyclic templates then provides an efficient access to stereodefined polyketides. We give here an overview of noniterative approaches to polyoxygenated compounds from 8-oxabicyclo[3.2.1]oct-6-en-3-one derivatives that are generated through [4+3] cycloaddition reactions.

2. [4+3]-Cycloadditions of Oxyallyl Cations to Furan and Derivatives

The generation of the 8-oxabicyclo[3.2.1]oct-6-en-3-one template can be achieved by a [4+3] cycloaddition of furan to oxyallyl cations of type 3 (Scheme 1). These stabilized cations **3** can be produced from tetrahalogenoketones **1** in the presence of a reducing metal[1] or a tertiary amine in an ionizing solvent.[2] The resulting rigid bicyclic system is a synthon of choice for stereoselective transformations as illustrated by the reduction of ketone **4**, with L-selectride or SmI_2 which provides the *endo*-alcohol **5** and the *exo*-alcohol **6**, respectively. In the late 1990s Vogel and co-workers extended this powerful strategy to a double [4+3] cycloaddition of 2,2-methylenebis(furan) **7** to oxyallyl cations which gives rise to a mixture of bis-bicycloadducts *meso*-**8** and *threo*-**8** in a 45:55 ratio (60% yield).[3] Several other precursors of oxyallyl cations were inves-



Scheme 1.

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tigated but the most efficient combination was tetrachloroacetone with triethylamine in HFIP. Expensive HFIP solvent can be replaced by toluene using 1,3-dibromo-1,3-dichloroacetone and Et_2Zn.[3]

Several examples of stereoselective functionalizations of these cycloadducts will be reviewed, in particular for the preparation of key subunits of biologically relevant natural compounds and analogues.

3. Synthetic Applications of 8-Oxabicyclo[3.2.1]oct-6-en-3-one

The 8-oxabicyclo[3.2.1]oct-6-en-3-one template was used to access a large variety of synthetically challenging fragments of natural products. The intrinsic rigidity of this core presents a real advantage and allows a high degree of stereoselectivity for functionalizations. But for those structures to be useful, the main challenge is to perform the desymmetrization of the *meso*-structure **4** in order to access the absolute configuration of the targets. The following examples will give an overview of the elegant methodologies that have been developed to transform 8-oxabicyclo[3.2.1]oct-6-en-3-one into valuable synthons for the preparation of natural targets and analogues.

Noyori *et al.*[4] already disclosed the high synthetic potential of bicyclic ketone **4** in 1978 for the synthesis of C-nucleosides. Those compounds, having a C–C ribosidic linkage instead of a C–N bond, display antibiotic properties as well as potent anticancer and antiviral activities.[5] For this synthesis a cinchonidine salt mediated resolution was accomplished in order to reach the absolute configuration of the natural product (Scheme 2).

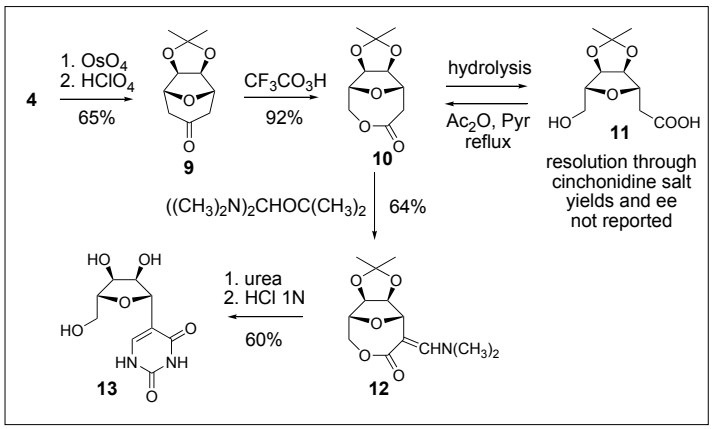
Treatment of the bicycloadduct **4** with H_2O_2 and a catalytic amount of OsO_4 furnished the corresponding *exo*-diol which was *in situ* protected as an acetonide. A subsequent Bayer-Villiger oxidation furnished racemic lactone **10** in high yield. For the desymmetrization, the saponified derivative **11** was reacted with enantiomerically pure cinchonidine. After separation of the diastereomeric salts, the optically pure ammonium salt was heated in a mixture of refluxing acetic anhydride and pyridine to regenerate the optically enriched lactone. Further elaboration involved the introduction of the dimethylaminomethylene moiety (2:1 *Z*:*E* ratio) to generate **12** as a common intermediate for the preparation of pyrimidine C-nucleosides. For instance, treatment with urea afforded, after removal of the acetonide moiety, the pseudouridine derivative **13**. This method was also applied to the production of pseudocytidine, 2-thiopseudouridine and chemotherapeutically significant pseudoisocytidine,[6] thus revealing the reliability of this synthetic route.

In recent years, C-glycosides have attracted much attention because of their similitude with the O-linked parents and their resistance to hydrolytic cleavage. The more stable C-glycosidic bond allows these derivatives to be developed as inhibitors of glycosidases and transferases. In view of the crucial involvement of these enzymes in metabolism defects, viral infection and cancer,[7] synthetic efforts have been reported for the generation of these sugar like structures. For instance, Masamune and co-workers[8] disclosed the use of Sharpless asymmetric epoxidation[9] as an alternative route to carbohydrate based synthesis[10] for the preparation of all eight L-configured hexoses starting from readily available (*Z*)-but-2-en-1,4-diol. Other routes toward a wide variety of sugars were proposed by Vogel and coworkers[11] starting from Diels-Alder adducts of furan. The 8-oxabicyclo[3.2.1]oct-6-en-3-one provided another synthon of choice and was exploited by Hoffmann *et al.*[12] to generate a set of C-glycosides presenting diverse configurations on the backbone. For that purpose, an asymmetric version of the dipolar [3+4] cycloaddition[13] was developed (Scheme 3).

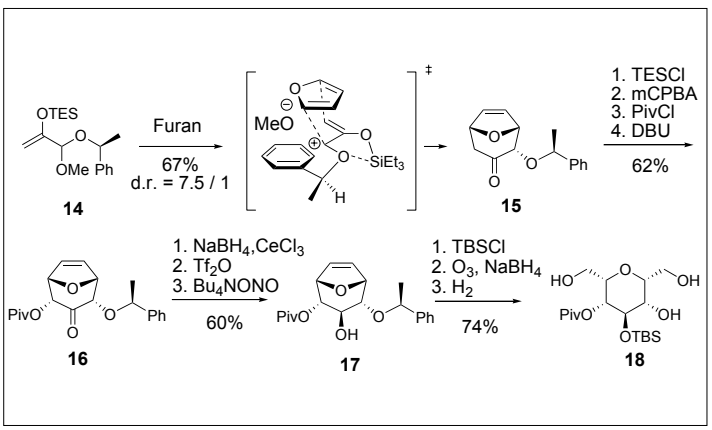
Chiral enol ether **14** derived from (*S*)-1-phenylethanol was ionized in the presence of a Lewis acid to provide a planar allylic cation that underwent diastereoselective cycloaddition with furan to furnish **15** (7.5:1 dr) in good yields. The intramolecular coordination of the silicon atom with the α-oxygen atom as well as π-stacking interaction rigidify the transition state and rationalize the observe diastereoselectivity. Further oxidation of the silyl enol ether with mCPBA[14] installed the axial α-hydroxyl group which was then acylated and epimerized under basic conditions to furnish **16**. Luche reduction[15] followed by displacement of the reactive triflate by tetrabutylammonium nitrite (Bu_4NONO) led to all equatorial hydroxyl groups. Completion of the synthesis was performed by oxidative cleavage of the olefin. The same methodology delivered the six other stereoisomers of this C-glycoside family.

Polypropionates and polyacetates are widespread structures in natural products[16] of biological interest. While asymmetric aldol reactions can offer a method of choice for the preparation of polypropionates, the stereoselectivity is generally poorer for the polyacetate category. One can access to this class of substrate through diastereoselective intramolecular reduction of β-hydroxy-ketones using for example Evans or Narasaka reductions.[17] Alternatively, the 8-oxabicyclo[3.2.1]oct-6-en-3-one core provides a rigid scaffold that can be efficiently converted into small polyketide subunits. The synthesis of the C(1)–C(7) fragment of bryostatins[18] is representative of this methodology (Scheme 4).

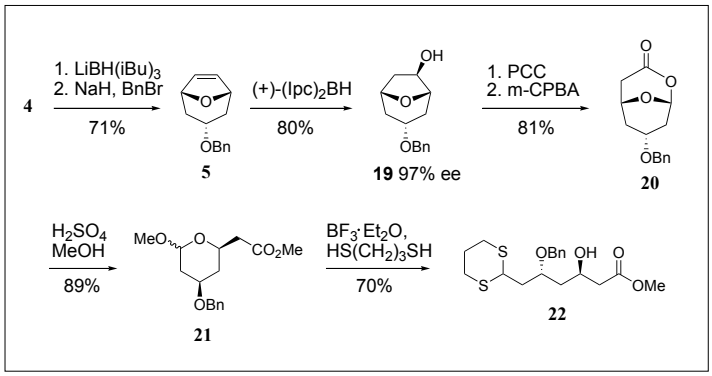
Benzyl ether **5** was submitted to asymmetric hydroboration[19] to deliver the corresponding alcohol **19** in high optical purity. A sequence of oxidation followed by Bayer-Villiger rearrangement and methanolysis of the resulting lactone installed the tetrahydropyran ring of **21**. Lewis acid promoted transthioacetalization with propane-1,3-dithiol afforded the semiprotected polyketide fragment **22**. Noteworthy, the adequate combination of the chiral boron



Scheme 2.



Scheme 3.



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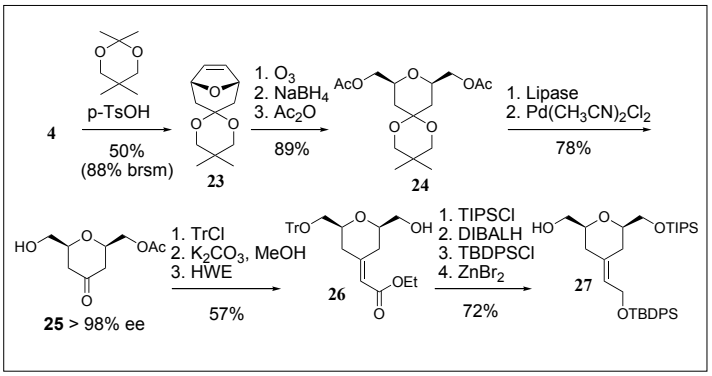
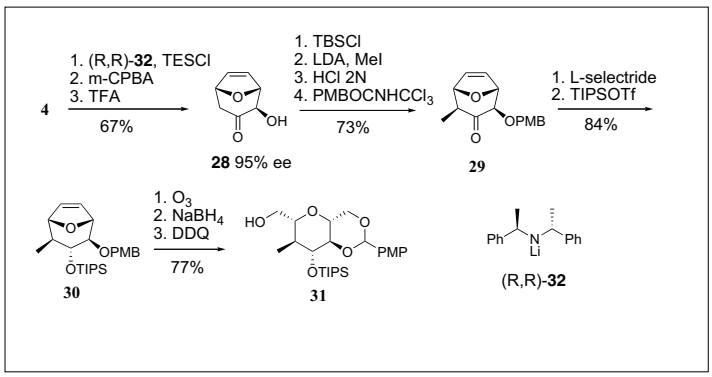


Scheme 5.



Scheme 6.

reducing agent and of the *endo* or *exo* starting alcohol can provide all stereoisomers of **22**.[20]

Enzymatic desymmetrization plays a growing role in organic synthesis and is also applicable to the 8-oxabicyclo[3.2.1]oct-6-en-3-one core,[21] as for example, toward the synthesis of the C(10)–C(16) fragment of bryostatins[22] (Scheme 5).

Protection of the ketone as a cyclic acetal followed by opening of the bicyclic structure using ozonolysis and reduction of the intermediate aldehydes gave, after protection, *meso*-diacetate **24**. A lipase PS (from *Pseudomonas cepacia*) promoted hydrolysis of one acetyl group was used to desymmetrize the *meso* structure and afforded, after liberation of the ketone, alcohol **25** in 98% enantiomeric excess. Further protecting group manipulations and Horner-Wadsworth-Emmons olefination delivered ester **26**. Reduction of the carboxylate completed the preparation of the C(10)–C(16) fragment of bryostatins. Recently this methodology was also applied to the synthesis of the C(1)–C(16) fragment of bryostatins.[23]

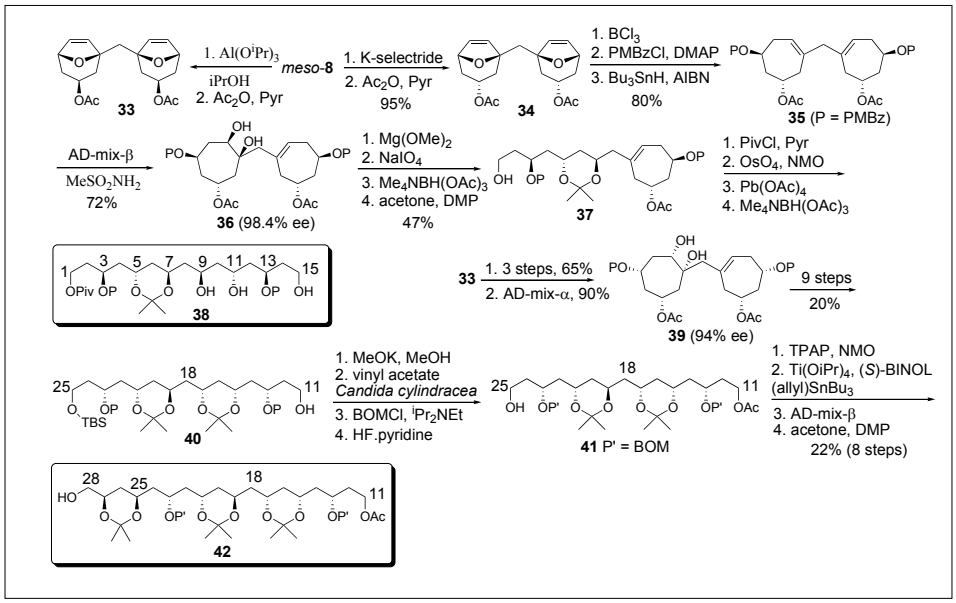
Among the diverse methods that have been developed for the desymmetrization of *meso* compounds, the use of enantioselective deprotonation is very useful. This strategy was applied on the 8-oxabicyclo[3.2.1] oct-6-en-3-one core for the synthesis of the C(38)–C(44) fragment of spongistatins[24] (Scheme 6).

Chiral base **32** was used to obtain the desymmetrized lithium enolate from ketone **4**, that was trapped as its triethylsilyl enol ether. Further Rubottom oxidation installed the *exo* hydroxyl group and delivered intermediate **28** with a 95% enantiomeric excess. Diastereoselective α-methylation of the carbonyl group followed by reduction set the last stereocenters to provide diol **30** as a unique stereoisomer. Oxidative cleavage of the olefin followed by trapping of the PMB oxidized cation by the free primary hydroxyl group afforded the semiprotected C(38)–C(44) fragment of spongistatins.

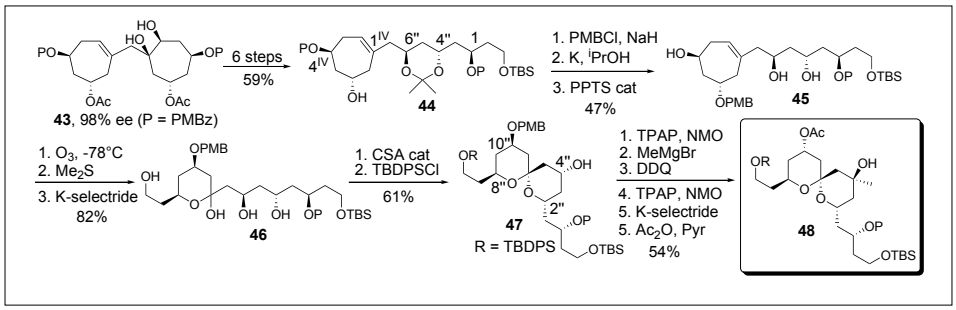
4. From 1,1'-Methylenedi(3-oxo-8-oxabicyclo[3.2.1]oct-6-ene) to Long Chain Polyketides and Analogues

The use of the 8-oxabicyclo[3.2.1]oct-6-en-3-one template as starting material for the preparation of polyketide-type derivatives finds a limitation in the length of the resulting skeleton that does not exceed seven carbon atoms. In order to develop efficient noniterative routes to longer fragments, Vogel and co-workers explored the stereoselective functionalization of di-ketones *meso*-**8** and *threo*-**8**. Interestingly, double reduction of *meso*-**8** using K-selectride or Merwein-Pondorf-Verley conditions led respectively to diacetate **33** and **34** with excellent stereocontrol (Scheme 7).[25] A SN_2'-type-8-oxa bridge cleavage induced by BCl_3, followed by esterification of the intermediate dichlorodiol and radical reduction provided diolefin **35**.[26] Desymmetrization was then achieved by means of the Sharpless asymmetric dihydroxylation to deliver the corresponding diol **36** with 98.4% enantiomeric excess. At that stage, the double elongation strategy proceeded through sequential sequences of oxidative opening of the seven-membered ring/diastereoselective reduction of the intermediate keto-aldehyde to provide a 15-carbon polyolic chain **38**. This protocol allowed complete control of the configuration of the newly formed diols at C(5),C(7) and C(9),C(11). Moreover, both primary alcohols can be differentiated through selective protection. By careful choice of the reducing conditions of the starting diketone *meso*-**8** and of the intermediate keto-aldehydes resulting from the opening of the cycloheptene rings, a large panel of stereoisomeric octols can be efficiently produced.[27] In addition, selective inversion of configuration of alcohols from intermediate **37** can give access, in principle, to all possible stereomeric pentadecane-1,3,5,7,9,11,13,15-octols.

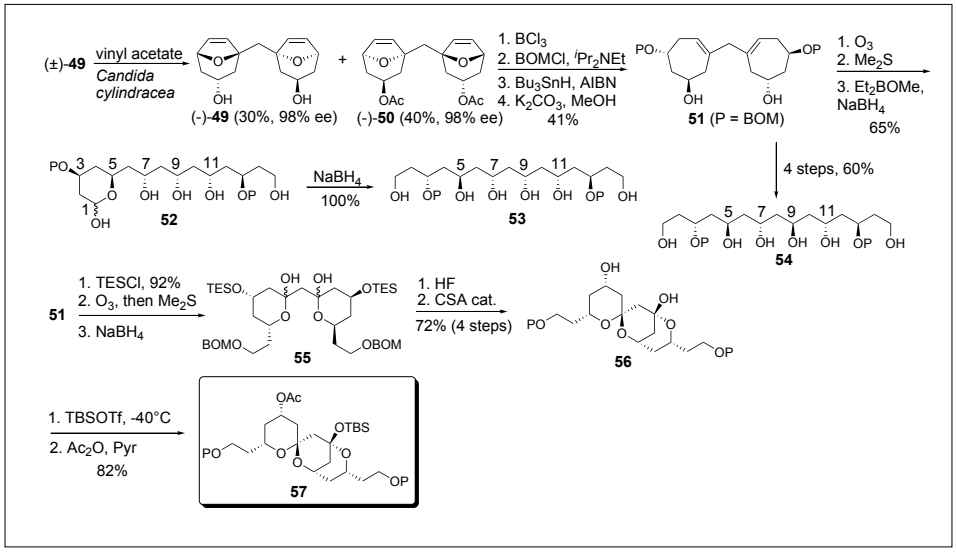
This versatile methodology was further applied to the synthesis of the polyolic subunit of the oxo-polyene macrolide RK-397.[28] The synthetic sequence started from diol **39** that was obtained with 94% enantiomeric excess through the Sharpless asymmetric dihydroxylation and involved two sequences of oxidative cleavage/diastereoselective reduction to install the C(15),C(17)-*syn*-diol and the C(19),C(21)-*anti* diol. A change of protecting groups was then operated on intermediate **40** to remove the *p*-methoxybenzoate, allowing further oxidation at C(25) and diastereoselective allylation under Keck conditions.[29] The resulting homoallylic alcohol was submitted to diastereoselective dihydroxylation in the presence of AD-mix-β to install the C(27),C(28) diol with a good 7:1 diastereoselectivity, thus completing the preparation of the C(11)-C(28) polyketide subunit of RK-397.



Scheme 7.



Scheme 8.



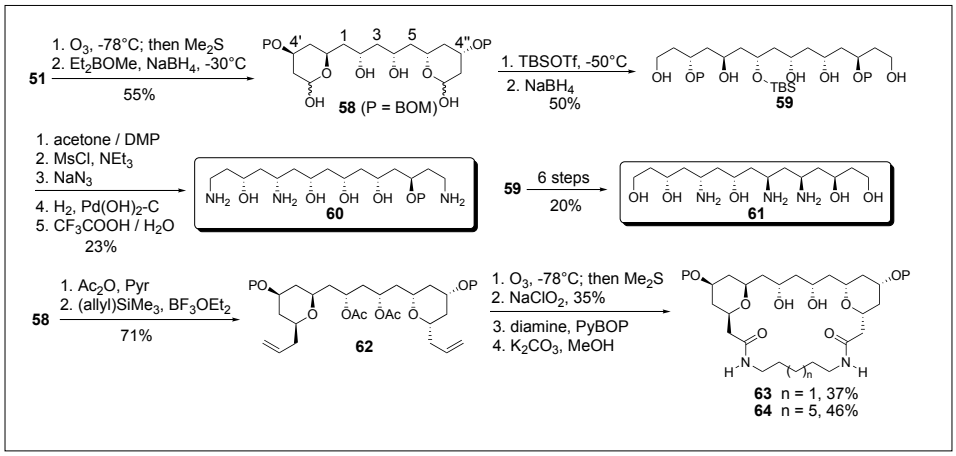
Scheme 9.

This strategy could also provide a rapid access to functionalized 6,6-spiroketals[30] and in particular to an advanced precursor of the AB spiroketal subunit of spongistatins,[31] a family of potent antitumoral marine macrolides. For that purpose the enantiomerically pure diol **43** was elaborated into the semi-opened system **44** (Scheme 8). Protection of the remaining secondary alcohol and selective removal of the C(4^{IV})-*p*-methoxybenzoate allowed oxidative opening of the cycloheptene ring and subsequent reduction with K-selectride to afford hemiketal **46** in high yield. Acid-promoted spirocyclization followed by silylation of the terminal alcohol delivered the functionalized spiroketal **47**. At that stage, the methyl carbinol moiety was installed at C(4'') and the C(10'') alcohol was inverted to provide the densely oxygenated spiroketal **48** as a precursor of the natural fragment.

The *threo*-diketone **8** was also efficiently valued through the enzymatic resolution of diol (±)-**49** to provide both enantiomers (−)-**49** and (−)-**50** in good yields and optical purity[32] (Scheme 9). Further elaboration of diacetate (−)-**50** delivered the semi-protected diol **51** which was submitted to a double ozonolysis followed by reduction of the intermediate ozonide and subsequent stereoselective reduction of the carbonyl moieties.[33] Interestingly, it was possible to isolate hemiketal **52**, thus offering a chemical desymmetrization of the long chain polyketide. Further reduction delivered hexol **53** which revealed the C(5),C(7)-*anti* and C(9),C(11)-*syn* configuration of the newly formed diols. Moving from Nazaraka's reducing conditions to Evans' borohydride afforded the *anti*,*anti*,*anti* tetrol at C(5),C(7),C(9),C(11) (**54**). This simultaneous functionalization of both cycloheptene rings offers a very short access to enantiomerically pure long chain polyketides.

Functionalized 1,7-dioxaspiro[5.5]undecanes could also be generated after silylation of the starting diene **51.**[34] Simultaneous ozonolysis of the olefins followed by reductive treatment afforded a mixture of bis(hemiketals) **55** which was directly treated under acidic conditions to cleave the silyl ethers and induce cyclization to the tricyclic hemiketal **56** in high yield (72%, four steps). Interestingly, this sequence provided the less energetically favorable kinetic axial/equatorial spiroketal by trapping in a tricyclic structure. Sequential protection of the free alcohols delivered the tricyclic spiroketal **5** as a potential template for further functionalizations.

From this methodology, it was possible to reach another type of biologically relevant derivative, the aminofunctionalized polyketides. Interestingly, by performing the sequence of ozonolysis/diastereoselective reduction on olefin **51** at low temperature, the bis(hemiketals) **58** were isolated in good yield[35] (Scheme 10). Regioselective silylation of the alcohol at C(2), followed by subsequent reduction of the hemiketal moieties afforded the semi-protected polyol **59** as a single isomer. This intermediate was then used for the selective introduction of amino groups on the polyketide skeleton by mesylation of the free alcohols, displacement with sodium azide and reduction of the azido group. A final acidic cleavage of remaining protecting groups delivered aminofunctionalized polyketides as exemplified by derivative **60** and **61**.



Scheme 10.

C-glycosylation of bis(hemiketals) **58** generated the bisallyl intermediate **62** that was used for a coupling reaction with diamine linkers to generate the macrocyclic structures **63** and **64** as cyclic glycolipid analogues.[36]

5. Conclusion

8-oxabicyclo[3.2.1]oct-6-en-3-one derivatives have demonstrated a very high synthetic potential for the development of noniterative routes to polyketide type compounds. From bicycloadduct **4** and bis(bicycloadducts) **8**, a panel of key fragments of natural products and analogues has been efficiently synthesized. Exploiting the stereoselectivity associated with the functionalization of rigid bicycles and diverse methods to generate optically pure synthons, the protocols reported above constitute a key contribution to asymmetric synthesis of complex molecules of biological interest starting from readily renewable sources (sustainable development).

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