Advances in the Synthesis of Calystegines and Related Products and their Biochemical Properties

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Abstract: The revision of the structures and properties of Calystegines shows that they can be regarded as carbohydrate mimics, with related biological activities and peculiar characteristics. Not only they can be isolated from food plants, but they can be obtained from a variety of monosaccharide derivatives and of non-carbohydrate products. Although several synthetic calystegine analogs have been reported as glycosidase inhibitors, new, more potent and effective inhibitors are required.

Keywords: Calystegine, Polydroxylated Nortropane, Polydroxylated Alkaloid, Glycosidase Inhibitor.

Dedicated to the memory of Professor Rafael Suau

INTRODUCTION

Calystegines are hydroxylated nortropane alkaloids firstly reported in 1988 from *Calystegia sepium* (Tepfer *et al.*) [1]. They were structurally characterized in 1990 (Goldmann *et al.*) [2]. All have a nortropane skeleton and several hydroxy groups in various positions. The hydroxy groups make the compounds hydrophilic; so, in usual alkaloid extraction procedures that contain a lipophilic extraction step, from an aqueous alkaline medium, they remain in the aqueous phase. That may explain why they were not found earlier. Their biosynthesis is related to the tropane alkaloid biosynthetic pathway and shares the first enzymatic steps [3]. Calystegines are strong glycosidase inhibitors [4-8] and occur in vegetables such as potatoes, tomatoes, aubergines and cabbage [7, 9]. The calystegines are common in the Solanaceae and there are several *Solanum* species which produce cases of poisoning [7]. It seems likely that the described syndromes are lysosomal storage disorders caused by glycosidase inhibition produced by the calystegines [10,11]. It was reported that calystegines have a role as nutritional mediators, i.e. they are excreted into the soil and attract bacteria that are in the rhizosphere of the plant [1].

STRUCTURE OF CALYSTEGINES AND RELATED PRODUCTS

The structures of natural calystegines are given in Fig. (**1**), (Table **1**) [3]. Calystegines are divided into three categories depending on the number of hydroxyl groups: trihydroxy derivatives form the calystegine A-group and tetrahydroxy and pentahydroxy derivatives form the calystegine B- and calystegine C- groups, respectively. As a common characteristic, they all contain a tertiary hydroxy group as part of hemiaminal functionality. Additionally, calystegine derivatives with an N-methyl group or an amino group, replacing the tertiary OH group, have also been isolated and named as calystegines [3, 13]. Trihydroxy- and dihydroxynortropanes [12] are not named calystegines, even though they derived from the same biosynthetic pathway (Fig. **2**, Table **2**). Glucopyranosides of calystegines have been isolated and identified [14] and new glycosides synthesized [15].

As regards to the structural requirements, it seems that the presence of the three axially-oriented substituents at the six-membered ring is hardly compatible with the existence of an hemiaminal center, which probably accounts for the fact that 3-epi-(+)-calystegine B_2 is the only diastereomer missing in the calystegine B natural compound series [16]. On the other hand, the equilibrium between the open and closed ring structure was shown to be dependent on the position and the stereochemistry of the hydroxy groups, but still it is not possible to determine systematically which structures isomerize and which do not [16, 17]. All naturally occurring calystegines showed a clear preference for the bicyclic structure, but ring-opening and isomerization cannot be excluded, and may contribute to the variety of calystegine structures. Several calystegine derivatives have been synthesized with diverse functionalization and new analogs with bigger ring sizes have been described [17] (Fig. **3**).

SYNTHESIS AND BIOLOGICAL ACTIVITY

The first reports of structure elucidation of calystegines and some related alkaloids, together with their occurrence in plant species, were referenced in a previous review [3]. The biosynthesis of calystegines was summarized in 1996 [7], and in 2004 [3], and since then the biogenetic pathway has received further experimental support [9, 20]. Their specific properties were emphasized in those reviews and in previous reports [21]. Less attention has been given to the chemical synthesis reviews, although chosen references were included in general calystegine chapters [3, 6, 22] or joined to syntheses of other tropane analogs [23].

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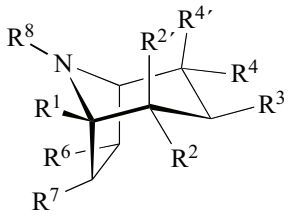
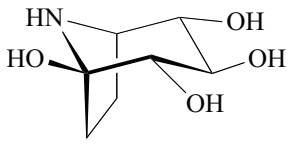




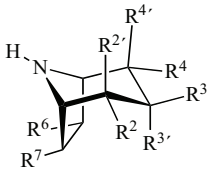
(+)-Calystegine B_2

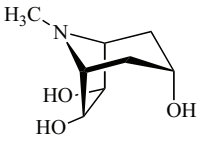
Fig. (1).

Table 1. Naturally Ocurring Calystegines

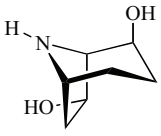
Calystegine	R^1	R^2	$R^{2'}$	R^3	R^4	$R^{4'}$	R^6	R^7	R^8
A_3	OH	OH		OH					
A_5	OH			OH	OH				
A_6	OH	OH						OH	
A_7	OH	OH				OH			
B_1	OH	OH		OH			OH		
B_2	OH	OH		OH	OH				
B_3	OH		OH	OH	OH				
B_4	OH	OH		OH		OH			
B_5	OH		OH			OH		OH	
C_1	OH	OH		OH	OH		OH		
C_2	OH		OH	OH	OH		OH		
N-Me-B_2	OH	OH		OH	OH				CH_3
N-Me-C_1	OH	OH		OH	OH		OH		CH_3
N_1	NH_2	OH		OH	OH				

Blank cells = No substituent.





Teloidine

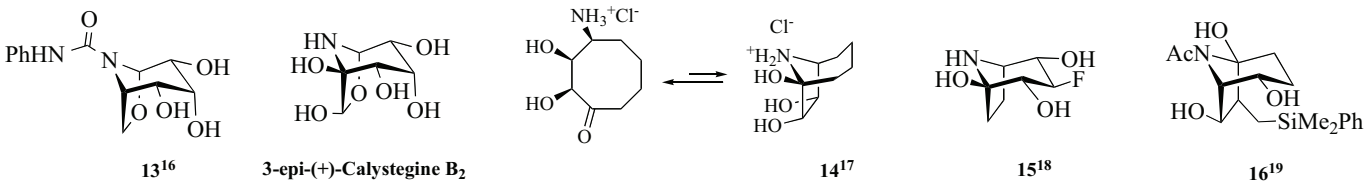


(-)-Erycibelline

Fig. (2).

Table 2. Trihydroxy- and Dihydroxynortropanes

	R^2	$R^{2'}$	R^3	$R^{3'}$	R^4	$R^{4'}$	R^6	R^7
1	OH		OH				OH	
2	OH		OH		OH			
3		OH	OH					
4			OH		OH			
5	OH		OH					
6					OH			OH
7			OH				OH	
8				OH			OH	
9					OH		OH	
10	OH							OH
11	OH		OH					
12				OH				OH



13[16] **3-epi-(+)-Calystegine B_2** **14**[17] **15**[18] **16**[19]

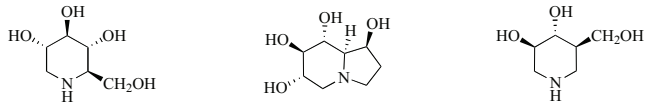
Fig. (3). Synthetic Nortropane and Calystegine Derivatives.

From the discovery of natural calystegines up to now, several synthetic approaches have been made. The first described syntheses are from 1992 [24]. Calystegine A_3 was synthesized as racemic mixture and enantiomerically pure (+) and (-)-calystegines B_2 were successfully prepared. In the following years several methodologies have been developed to target calystegines. Thus, the byciclic structures were obtained by ring closing methatesis (RCM) [25-28], ring expansions [29, 30, 31] cycloadditions, [32-34], radical cyclization [26] and polar cyclization [35, 36]. Enzymatical resolution was also developed [37].

There is a natural connection between carbohydrates and calystegines. Calystegine accumulation in root cultures was described to increase with carbohydrate availability [9]. Consequently, and in conection with the biosynthesis of calystegines, it is logic to develop syntheses with monosaccharides as starting materials. On the other hand, the shape and asymmetric centers of calystegines remember those of the monosaccharide derivatives. The availability of a wide range of carbohydrates as sources of enantiopure building blocks might provide much of the required functionalization and stereochemistry. Several syntheses from monosaccharide derivatives have been reported and several of them listed in reviews [7, 22, 23].

In this revision, we will mainly focus on the last calystegine syntheses from carbohydrates but without forgetting references to chosen methods from non-carbohydrate precursors, and those that were not previously collected in other specific reviews. We will also take account of the inhibitorial properties of the new compounds.

Glycosidase inhibitory activities in addition to possible medical applications can be expected for calystegines and hydroxynortropanes because they can be considered as piperidinic iminosugars with an ethylene or hydroxy ethylene bridge between the 1,5-carbons. Biochemical activities and therapeutic applications of calystegines and analogs have been reported [22, 38, 39, 40] or included in reviews on glycosidase inhibitors and polyhydroxylated alkaloids [7, 8, 21, 41]. In contrast to monocyclic iminosugars (pyrrolidines and piperidines) and bicyclic (pyrrolizidines and indolizidines) which have been extensively exploited in the field of glycosidase inhibition [4, 5, 42], calystegines have been less explored and only several ring-modified calystegine analogs have been reported [16, 35, 43-45]. Glycosidases are involved in a broad range of biological events [46, 47] and therefore, inhibitors of these enzymes have potential in therapies related to cancer [48, 49], viral infections [50], diabetes [51], tuberculosis [52] and glycosphingolipid storage disorders [4]. But, molecular basis for glycosidase inhibition by the calystegines remain poorly understood [53]. Structural and mechanistic studies on a β-glucosidase showed unambiguously that calystegine B_2, one of the most powerful representatives, binds at the active site in an orientation with the nitrogen atom at the position of the anomeric carbon in a native glycoside [54, 55]. While in the case of 1-deoxynojirimycin (**17**) and castanospermine (**18**) (Fig. **4**), the nitrogen atom is at the position where O5 is found in the native glycoside substrate. In this sense, B_2 might be regarded as an analog of the potent β-glucosidase inhibitor isofagomine (**19**) [56]. Screening of a variety of natural and synthetic alkaloid compounds showed isofagomine, *N*-dodecyl deoxynojirimycin, calystegines A_3, B_1, B_2 and C_1, and 1,5-dideoxy-1,5-iminoxylitol to be potent inhibitors of glucocerebrosidase [57]. Among them, isofagomine was the most potent inhibitor of glucocerebrosidase *in vitro*.



1-deoxynojirimycin (17) **castanospermine (18)** **isofagomine (19)**

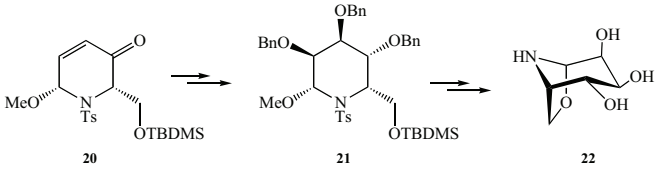
Fig. (4). Glycosidase Inhibitors with Structure of Iminosugar.

The inhibitory activity of calystegines and other polyhydroxylated alkaloids is generally restricted to exoglycosidases cleaving at the non-reducing end of a saccharide chain, while endoglycosidases that cleave within a saccharide chain releasing oligo-or disaccharides mostly remain unaffected [58]. Calystegines B_1 and C_1 are strong inhibitors of β-galactosidase [7]. Inhibitory activities of other natural calystegines have been reviewed, showing competitive or non-competitive inhibition depending of the type of enzyme or the structure of the polyhydroxylated alkaloid [3]. Comparison of the extent of the inhibitory reactivity with variation in structure or stereochemistry allowed broad conclusions [7]. The inhibition is often pH-dependent and it has been suggested that the alkaloids inhibit by the formation of an ion pair between the protonated inhibitor and an anionic group, probably a carboxylate anion, in the active site [4]. Recently, calystegine B_3 has been reported as a potent specific inhibitor for rat liver cytoplasmic Man2C1 activity [59]. The suppression of Man2C1 expression induces apoptosis in various cell lines, but its molecular mechanism remains unclear.

SYNTHESIS OF CALYSTEGINES AND ANALOGS FROM CARBOHYDRATE DERIVATIVES

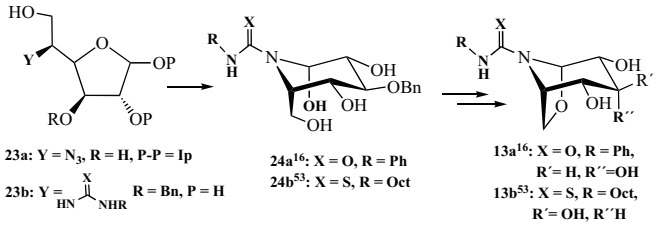
Several syntheses of polyhydroxylated 6-oxa-nortropanes have been reported [16, 35, 43, 44]. Compound **22,** a

calystegine B_4 analog [35] was obtained from a chiral (2*S*)-2-(hydroxymethyl)dihydropyridone **20,** easily accessible from D-glucal. The cyclization to the second ring (Scheme **1**) was achieved after five steps by addition to an immonium intermediate in the presence of hydrides.



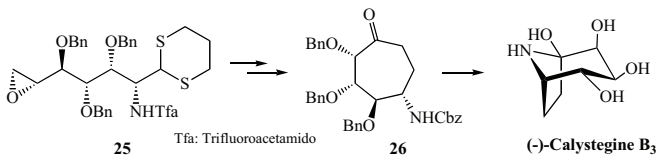
Scheme (1).

The group of Ortiz-Mellet and García-Fernández reported [16, 53] syntheses of polyhydroxylated 6-oxa-nortropanes **13** from 5-azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose **23a** (Scheme **2**), readily accessible from commercial glucuronolactone. The synthetic strategy involves the furanose/piperidine rearrangement of 5-deoxy-5-ureido-L-idose precursors (**23b**), followed by intramolecular glycosylation involving the primary hydroxyl group. Inversion of the configuration at C-3 [16], in the resulting 6-oxa-(+)-calystegine B_2 analog, allows accessing the elusive 3-epi-6-oxa-(+)-calystegine B_2 skeleton of **13a**. Acid-catalyzed opening of the nortropane bicycle was observed, but could be avoided by careful neutralization of the reaction mixture. The inhibition results suggest that (+)-calystegine B_2 derivatives and the corresponding C-3 epimers can be seen as glucomimetics and galactomimetics, respectively, pointing to a 1-azasugar mode of action for this family of alkaloids. Structural and mechanistic studies of the interactions of **13b** with the active-site of the clan GH-A β-glucosidase *Tm*GH1 (from *Thermotoga maritima*), showed an orientation with the bridge below the plane of the glycoside ring and with the alkyl substituent projecting into a channel lined with a number of hydrophobic residues [53, 54].



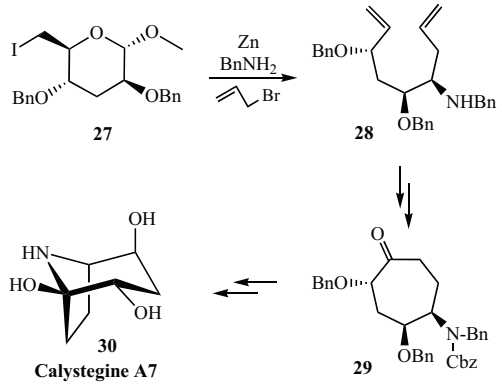
Scheme (2).

The enantiomer of the natural (+)-calystegine B_3 was synthesized [36] from a D-glucosamine trimethylene dithioacetal derivative. The sequence started with oxidation to the 6-aldehyde, followed by an epoxy heptose ditioketal formation (**25**), and a cyclization by epoxide opening. The six and seven-membered ring amino carbasugars could be produced, although the desired cycloheptane in less proportion. After functionality changes with the formation of an amino cycloheptanone, cyclization to (-)-calystegine B_3 was accomplished by catalytic hydrogenation (Scheme **3**).



Scheme (3).

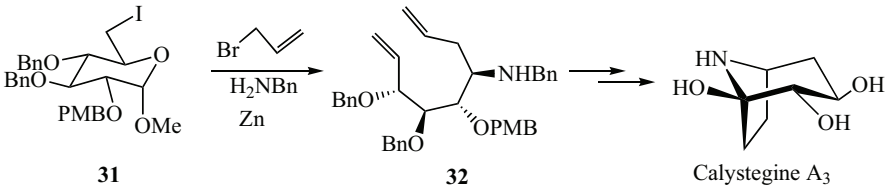
A methodology developed by Madsen *et al.* to get several calystegines (B_2, B_3, and B_4) started with methyl 6-iodo-monosaccharide derivatives and included an ultrasound assisted Zn-mediated tandem ring opening reaction, followed by a Grubbs'catalyst mediated RCM, hydroboration and oxidation [27, 28]. Following this strategy, Calystegine A_7 was obtained by Csuk [60] from methyl α-D-glucopyranoside *via* a 3-deoxy-6-iodo derivative (**27**, Scheme **4**). In a preliminary test, calystegine A_7 showed a K_i value (β-glycosidase from almonds) of 2.1 mM as compared to a K_i for calystegine B_2 of 5.9 mM.



Scheme (4).

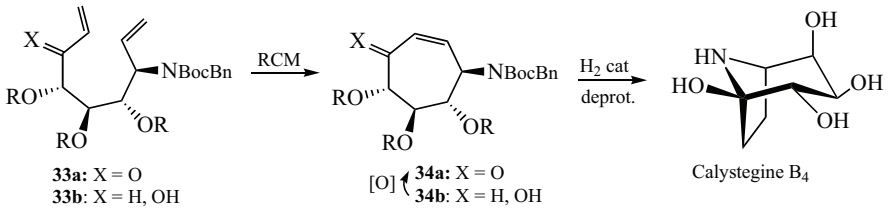
More recently [61], a non-natural calystegin, 3-epi-calystegine-B_2 (Fig. **3**), was similarly synthesized by this group. Compared to calystegin B_2, the target compound is no longer an inhibitor for a β-glycosidase hence proving that an equatorial OH group at position C-3 is necessary for a tight binding of calystegins into the active site of β-glycosidases. Using analogous key steps, the first total synthesis of a fluorinated calystegin A (**15**, Fig. **3**) was described [18]. The fluorinated compound is a selective and competitive β-glycosidase inhibitor.

Calystegine A_3 was prepared in 13 steps from D-glucose [62]. The benzyl protected methyl 6-iodo glucoside **31** was converted into a 4-benzylaminonona-1,8-diene **32**. Subsequent RCM yielded the corresponding cycloheptene. Deoxygenation by the Barton–McCombie protocol, hydroboration and oxidative workup followed by hydrogenolysis afforded calystegine A_3 (Scheme **5**). The methodology based on RCM reaction was improved by Pyne *et al.* [63]; the total synthesis of calystegine B_4 was achieved in 10 steps from (–)-D-lyxose by using a new synthetic strategy to obtain the requisite protected hydroxylated 4-aminocyclohept-2-en-1-one without the problem of regioisomer formation that occurred in the earlier synthesis



31 **32** Calystegine A_3

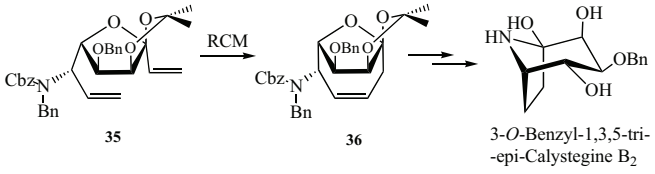
Scheme (5).



Scheme (6).

of this natural product. The key steps included a Petasis–borono-Mannich reaction previous to the RCM reaction (Scheme **6**).

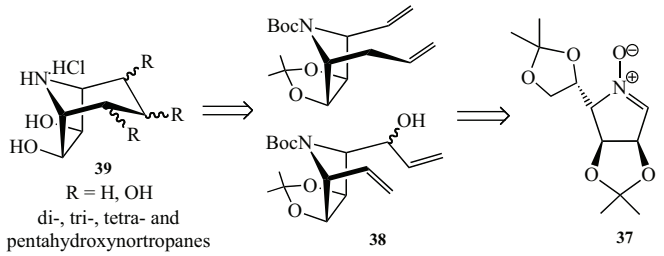
A different strategy [64] using RCM reaction started from L-sorbose. The 3-*O*-benzyl derivative of the polyhydroxylated nortropane alkaloid 1,3,5-tri-*epi*-calystegine B_2 was prepared by a Wittig and magnesium-mediated alkylation methodology, followed by the RCM reaction, under microwave irradiation (Scheme **7**).



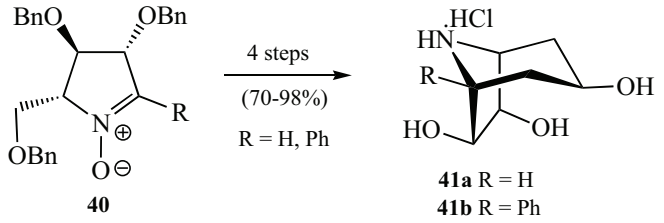
Scheme (7).

Diverse published syntheses start from nitrones: Shing [65], Kaliappan [40], and Goti and Merino [66] have used nitrones obtained from monosaccharides as intermediates in the synthesis of calystegines. The bicyclic system was formed by intramolecular nucleophilic attack of nitrogen to a keto group in the last step. Kaliappan reported the synthesis of calystegine analogs based on addition of unsaturated organometallics to a cyclic mannose-derived nitrone (**37**). Subsequent RCM provided intermediates in the synthesis of several calystegine analogs (**39**) either by syn-dihydroxylation or by hydrogenation and followed by global deprotection (Scheme **8**). Interestingly, two of the compounds exhibited significant noncompetitive inhibition against α-mannosidase and *N*-acetyl-β-D-glucosaminidase.

Starting from a different nitrone **40** obtained from D-arabinose, two new polyhydroxylated nortropane calystegine analogs **41a** (R = H) and **41b** (R = Ph) (Scheme **9**) were recently prepared in excellent yields and complete selectivity [66]. The synthetic strategy was based on consecutive nucleophilic allylation, oxidation and intramolecular dipolar cycloaddition. The key intermediate cycloadducts formation took place through a 2-aza-Cope rearrangement of nitrones.



Scheme (8).



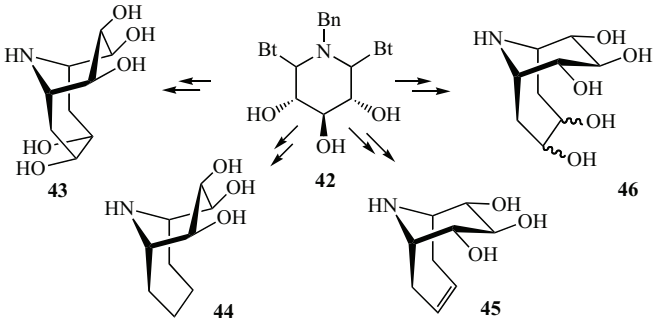
Scheme (9).

New calystegine analogs, namely polyhydroxylated 10-azabicyclo[4.3.1]decanes (Scheme **10**) were obtained from a trihydroxylated 2,6-bis(benzotriazolyl)piperidine starting from D-glucose (**42**). A double benzotriazolyl/carbon nucleophile exchange followed by a ring-closing metathesis led to the bicyclical structures in a rapid and stereodivergent synthesis. These compounds were subjected to a preliminary evaluation as inhibitors of β-glucocerebrosidase and the pentahydroxy compound **43** showed an IC_{50} value in the micromolar range similar to the one observed for 1,5-dideoxy-1,5-iminoxylitol [67]. In addition, compound **43** was found to be a quite potent inhibitor of almond β-glucosidase.

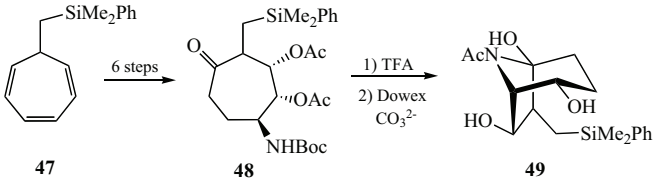
SYNTHESIS FROM NON-CARBOHYDRATE DERIVATIVES

A route to silyl-homocalystegines and homocalystegines (Scheme **11**), in 7 and 8 steps respectively, from a commercially available tropylium salt **47** was designed according to recent studies on the desymmetrization and functionalization of silylmethylcycloheptatrienes [19]. An

unexpected rearrangement, likely resulting from a thermodynamically driven intra- and intermolecular acetate group migration was described. For biological activity screening purposes, it may also be interesting to keep the silicon group in the final target as this lipophilic group has been shown recently to enhance the activity in certain cases [68].



Scheme (10).

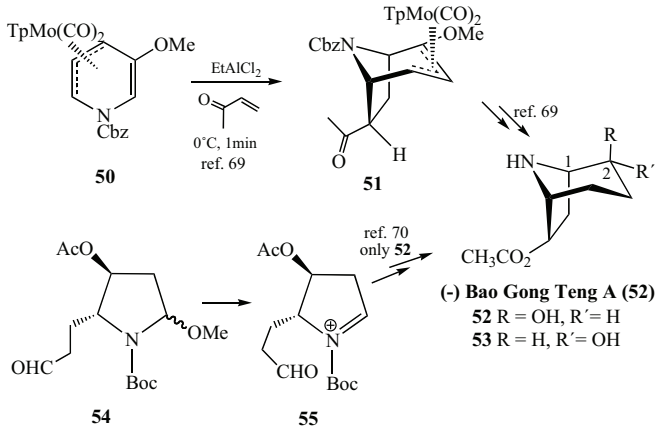


Scheme (11).

(-) Bao Gong Teng A, an acetylated dihydroxytropane isolated from the Chinese herb Erycibe obtusifolia Benth, was synthesized by an "organometallic chiron" strategy [69]. Single enantiomers of TpMo(CO)2(η^3-pyridinyl) complexes were produced and transformed by a stereocontrolled [5+2] cycloaddition to methyl vinyl ketone and further demetalation to intermediates possessing the tropane core, which generated (-) Bao Gong Teng A (**52**) and its 2-epimer **53** (Scheme **12**), in a stereodivergent strategy. The natural product **52** has hypotensive and miotic activity and has been used for the treatment of the glaucoma. Recently, a new enantioselective synthesis of (-) Bao Gong Teng A has been reported [70]. The method features a new intramolecular reductive coupling reaction of *N,O*-acetal with aldehyde **54**, cooperatively mediated by $BF_3.OEt_2$ and SmI_2.

CONCLUSIONS

The potential pharmaceutical benefits of polyhydroxylated alkaloids as anti-viral and anti-cancer agents appear to largely result from their ability to alter glycoprotein structure by interfering with processing of the oligosaccharide moiety. But, it has been found that the doses required for beneficial effects may be below those causing damage, or that allowing a period of clearance between doses may limit toxicity [8]. However, there are differences in the observed inhibition of liver glycosidases by calystegines, depending on each mammalian group. More calystegine analogs are still requested, especially those designed on structure-activities studies, although many aspects of their biochemical properties are yet unknown [53]. The increasing number of syntheses of calystegine analogs from carbohydrate derivatives opens the door to new, more potent and effective glycosidase inhibitors.



Scheme (12).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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