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(–)-Isosteviol as a Versatile Ex-Chiral-Pool Building Block for Organic Chemistry

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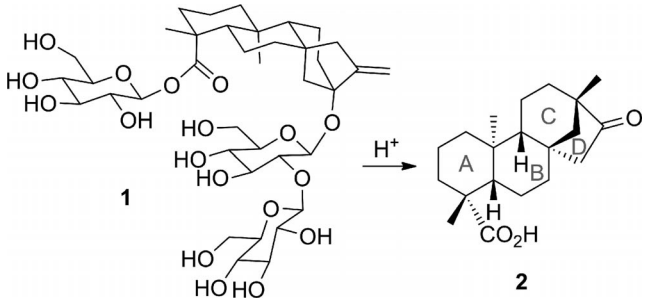
(–)-Isosteviol is readily available in large quantities by the acidic treatment of a common alternative sweetener. The two functional groups of (–)-isosteviol are presented on the same side of the *ent*-beyerane scaffold with a mutual C–C distance of about 7 Å. Their unique concave arrangement experiences a strong asymmetric environment due to an adjacent methyl group. Consequently, this building block has found several applications in supramolecular chemistry and organocatalysis. These areas and the chemical modification of this scaffold as well as its biological activity are surveyed.

1. Introduction

The diterpenoid glycoside stevioside (**1**; Scheme 1) has been isolated as the major component from the leaves of the *stevia* plant (*stevia rebaudiana* Bertoni) along with a variety of minor glycosides that differ in the number and nature of attached glucose moieties.[1] Stevioside has been widely used as a noncaloric artificial sweetener in Asia and South America due to its greatly enhanced sweetness (more than 300 times sweeter) compared with "standard" cane sugar sucrose.[2] Stevioside has recently come into focus again, having been accepted as a sugar substitute in the EU as well.[3] Apart from its sweetening properties, stevioside and its derivatives exhibit a large number of cytotoxic and biological activities, including antihyperglycemic, antihypertensive, anti-inflammatory, antitumor, antidiarrheal, and immunomodulatory effects.[4]

The treatment of stevioside (**1**) with strong acids, for example, hydrobromic acid, cleaves the glucose fragments and renders, by the formation of a nonclassical cation, the natural diterpene (–)-isosteviol (**2**; Scheme 1). The diterpene **2** can be easily prepared by this cleavage method on a very large scale of up to several hundred grams (see the Supporting Information).[5,6]

(–)-Isosteviol (**2**), being a metabolite of stevioside, also exhibits a wide range of biological activities, which might be the reason why the EU has reluctantly accepted stevioside as an alternative sweetener. Compound **2** can induce insulin regulation[7] and exhibits cardioprotective[8] as well as cytotoxic[9] and antibacterial effects.[10] During the past few years, (–)-isosteviol has become a focus in organic chemistry for two major reasons. First, a large number of (–)-isosteviol derivatives have been shown to exhibit significantly higher biological activities than (–)-isosteviol itself,[10,11] leading to ongoing research for further new derivatives of **2** with possible applications in medicinal chemistry. Secondly, (–)-isosteviol is a unique building block in organic synthesis due to its quite rare structural features,[12] the concave array of the carboxylic acid and keto functions, which deviate from a parallel orientation by about 60°. This leads to a lipophilic skeleton and hydrophilic moieties on one side of the molecule (Figure 1), thereby representing an almost Janus-type architecture.



Scheme 1. Formation of (–)-isosteviol (**2**).

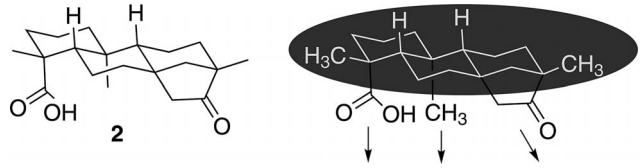


Figure 1. Unique structural features of (–)-isosteviol (**2**).

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2. Chemical Transformations

Because of the hydrocarbon nature of most parts of the (–)-isosteviol architecture, the standard repertoire of organic chemistry allows transformations at a limited number of positions. Thus, the 15-, 16-, and 19-positions (Figure 2) are prone to chemical conversion.

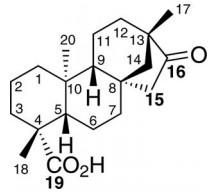

Figure 2. *ent*-Beyerane skeleton of (–)-isosteviol (**2**).

However, in spite of the limited number of reactive positions in (–)-isosteviol, a variety of methods can be employed to synthesize a large number of derivatives. The initial driving force for the synthesis of most of the following (–)-isosteviol derivatives (unless stated otherwise) was the possible application of these substrates in medicinal chemistry. Thus, an enormous number of the modified structures presented herein have been tested for their cytotoxic activities and biological properties. In this review, individual transformations are grouped into reactions occurring at specific rings of the *ent*-beyerane skeleton. The stereoselectivities of these transformations have in several cases been proven by X-ray analyses, the structural confirmation by NMR spectroscopic data in most cases being less reliable because their signals and/or coupling constants have not been assigned.

2.1. D-Ring Modifications

The five-membered ring of (–)-isosteviol, which contains the keto function, is defined as ring D of the *ent*-beyerane skeleton. Because this keto group is not sterically congested and is the most reactive moiety in the molecule, many conversions of (–)-isosteviol target this part of the molecule. Starting from (–)-isosteviol itself (Scheme 2, R = H) or its esters **3** or **4** (R = Et, Me), variously functionalized derivatives are directly accessible.

Stereoselective reduction of the keto function of **2** or **3** with sodium borohydride in ethanol yields the corresponding alcohols **5**, with the hydroxy function pointing downwards to give the (16*R*)-configured product;[10,13] the configuration was elucidated by X-ray analysis.[11] The stereoselectivity can be rationalized by the unique three-dimensional architecture of isosteviol. Attack of the hydride takes place from the convex side of the molecule due to increased steric demand by the methyl group (at the 20-position). This leads to the depicted (*R*) configuration.[11]

Bromination at the α-position relative to the carbonyl of **3** can be achieved by treatment with an excess of bromoethane/DMSO under basic conditions.[14] The depicted

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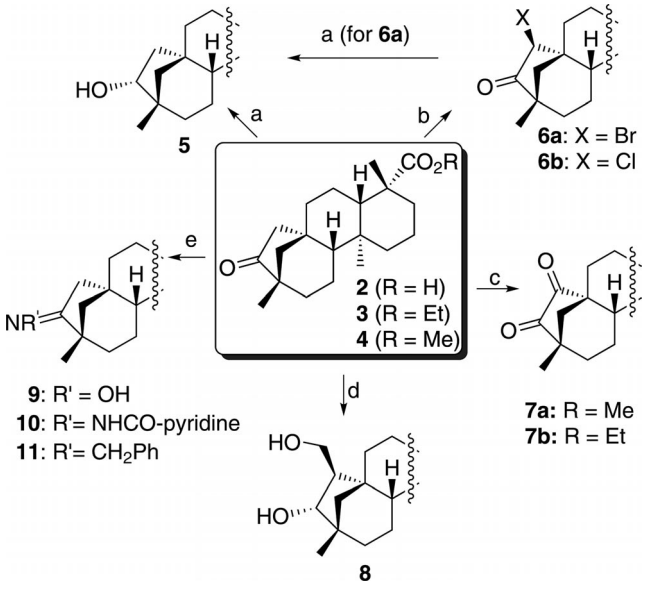


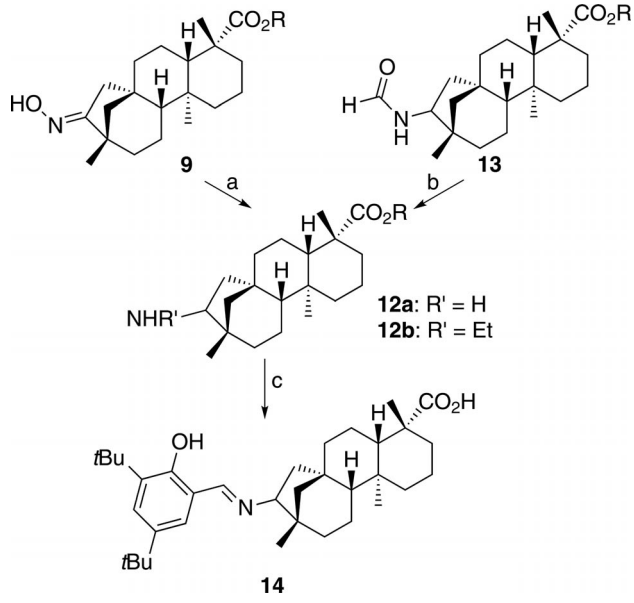
Scheme 2. Transformations of (–)-isosteviol (**2**). Reagents and conditions: a) $NaBH_4$, EtOH, 0 °C, 1 h, 92% (R = H)/96% (R = Et)/96% (from **6a**); b) X = Br: EtBr, DMSO, KOH, 80 °C, 3 h, 96% (R = Et); X = Cl: SO_2Cl_2, $CHCl_3$, 60 °C, 30 h, 97% (R = H); c) SeO_2, xylene, 145 °C, 2 d, 80% (R = H)/85% (R = Me)/Ac_2O, SeO_2, reflux, 6 h, 83% (R = Et); d) HCHO, NaOH (R = H)/NaOEt (R = Et), EtOH, 60 °C, 1 h, 95% (R = H)/3 h, 90% (R = Et); e) R′ = OH: $HONH_3Cl$, $NaHCO_3$, EtOH, 60 °C, 2 h, 90% (R = H)/95% (R = Et); R′ = NHCOPyridine: Pyr-$CONHNH_2$, *p*TsCl, MeOH, 6 h, 60–85%; R′ = CH_2Ph: $PhCH_2NH_2$, 4 h, 95 °C, 40% (R = H).

stereochemistry is based on analogous transformations.[15] Surprisingly, the reduction of brominated substrate **6a** with sodium borohydride again leads to the formation of debrominated alcohol **5**.[14] Alternatively, bromination can be accomplished by employing the standard mixtures of Br_2/AcOH or Br_2/HBr, yielding the desired product in quantitative or 80% yield, respectively.[16] The corresponding chlorinated derivative **6b** can be obtained in 97% yield by treating (–)-isosteviol (**2**) with sulfuryl chloride in chloroform. The stereochemistry of these conversions was verified by crystallographic analyses.

The introduction of a second keto function adjacent to the existing one can be achieved by Riley oxidation[17] of (–)-isosteviol or its methyl[18–20] or ethyl ester[21] by using selenium dioxide as oxidant (Scheme 2). The corresponding diketones **7** are of bright orange color. Diol derivative **8** (15*R*,16*R*) can be synthesized by a one-pot Tollens reaction ("one-pot aldol Cannizzaro reaction") by adding formaldehyde to a basic mixture of **2** or **3** in ethanol.[10,11,14] To avoid hydrolysis of the ester moiety, sodium ethoxide instead of sodium hydroxide was used when using the (–)-isosteviol ethyl ester.[22]

The keto moieties in **2**–**4** can also be transformed into various nitrogen-based functionalities (Scheme 2). The corresponding *E*-oximes **9** can be obtained in very good yields by the reaction of **2** or **3** with hydroxylamine hydrochloride.[14] Hydrazone derivatives **10**, like the pyridinecarbonyl-substituted compounds with the nitrogen atom located at all possible positions in the pyridine ring (R′ = NHCOPyr), can be formed from the corresponding hydrazides. Thus, reaction of **2** or **4** with pyridinecarbonylhydrazides and *p*TsCl in methanol provides the corresponding hydrazones in good-to-excellent yields.[23,24] Furthermore, the reaction of **2** with benzylamine under solvent-free conditions gives access to imine derivative **11** in moderate yields.[25]

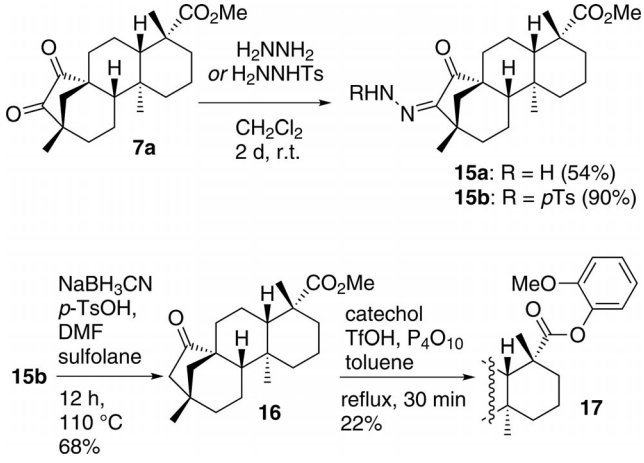
Most of the derivatives of (–)-isosteviol depicted in Scheme 2 serve as substrates for subsequent modifications. Oxime derivatives **9** (Scheme 3, R = H, Et) can be reductively converted into the amines **12a** by employing nickel metal as catalyst in THF under hydrogen.[14] Interestingly, when the reaction takes place in ethanol instead of THF, ethylamine **12b** is formed as the major product. Alternatively, amines **12a** can be obtained when formamides **13** (R = H, Me) are heated at reflux under basic conditions.[26] Compound **13** itself is formed by heating (–)-isosteviol or its methyl ester with excess formamide in formic acid. Amine **12a** (R = H) can subsequently be transformed into Schiff base derivative **14** by the reaction of the amine moiety with the appropriate benzaldehyde under basic conditions. A variety of substituents on the salicylaldehyde component are compatible, including a nitro or *tert*-butyl group at the *para* position, respectively.[26] Although the individual reports do not discuss it in detail, the stereocenter at the 16-position is not formed with good stereoselectivity, but usually as a mixture of diastereomers that are difficult to separate.



Scheme 3. Synthesis of Schiff base derivatives at the 16-position. Reagents and conditions: a) R′ = H: Ni, H_2, THF, 40 °C, 2 h, 82% (R = H)/88% (R = Et); R′ = Et: Ni, H_2, EtOH, 40 °C, 2 h, 86% (R = Et); b) $HCONH_2$, HCO_2H (90%), 18 h, 170 °C, 90% (R = H)/6 h, 190 °C, 51% (R = Me); c) NaOMe, MeOH, 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, 6 h, 20 °C, 60% (R = H).

A shift in the keto function in the methyl ester **4** of isosteviol from the 16- to the 15-position was first reported by Waldvogel and co-workers in 2008.[18] As described above (Scheme 2), Riley oxidation[17] of the (–)-isosteviol methyl

ester renders diketo derivative **7a** (Scheme 4). Subsequent conversion with hydrazine hydrate or *p*-tosyl hydrazine selectively yields the corresponding derivatives **15a** and **15b** with the newly introduced diazene moiety located at the sterically less hindered 16-position.



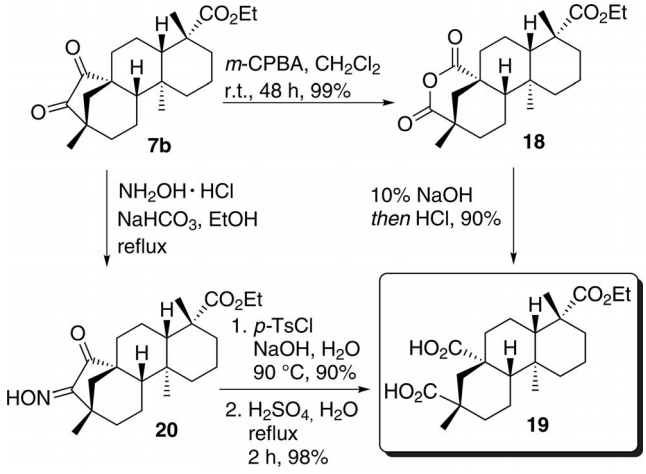
Scheme 4. Shift of the keto function in (–)-isosteviol and subsequent insertive esterification.

Wolff–Kishner reduction of **15a** did not lead to the formation of the desired product **16**. Therefore, the more reactive hydrazone **15b** was prepared and subjected to reduction. Thus, **16** was obtained in a yield of 68% by using cyanoborohydride as the reducing agent in the presence of *p*-toluenesulfonic acid in a mixture of DMF and sulfolane.[27] With the aim of synthesizing novel building blocks for the construction of optically active triphenylene ketals, **16** was then subjected to ketalization with catechol. However, it turns out that steric hindrance in the vicinity of the keto function at the 15-position prevents the ketalization reaction. Instead, an unprecedented insertive esterification occurred, leading to the formation of the guaiacol ester **17**.[18]

Oxidation of the diketo derivative **7b** under Baeyer–Villiger conditions was carried out by Zhang and coworkers.[21] The corresponding ring-expanded anhydride **18** (Scheme 5) was obtained in almost quantitative yield. Subsequent hydrolysis renders the monoprotected tricarboxylic acid **19** in 90% yield.

Alternatively, **19** can be obtained by the intermediate formation of the oxime **20** and subsequent Beckmann fragmentation of the ketoxime, induced by *p*-toluenesulfonic acid. The corresponding nitrile was isolated from this mixture. Acidic hydrolysis of the cyano group led to the formation of dicarboxylic acid **19**. Upon saponification of the ester moiety, molecules bearing three carboxylic acid functions in a concave arrangement and in close vicinity to each other might be accessible. Substrates with such a substitution pattern might then find application as surface-active agents for possible reactions at phase boundaries. All the acid functions are oriented almost in parallel and represent a chiral alternative to Kemp's triacid.[28]

A series of subsequent modifications can be readily made to the alcohol derivative **5** of (–)-isosteviol (Scheme 6).

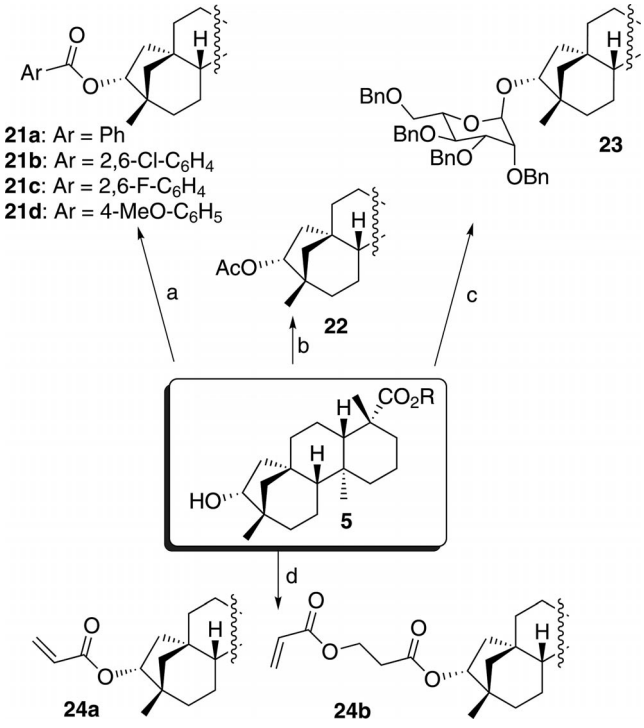


Scheme 5. Two possible pathways for the synthesis of **19**.

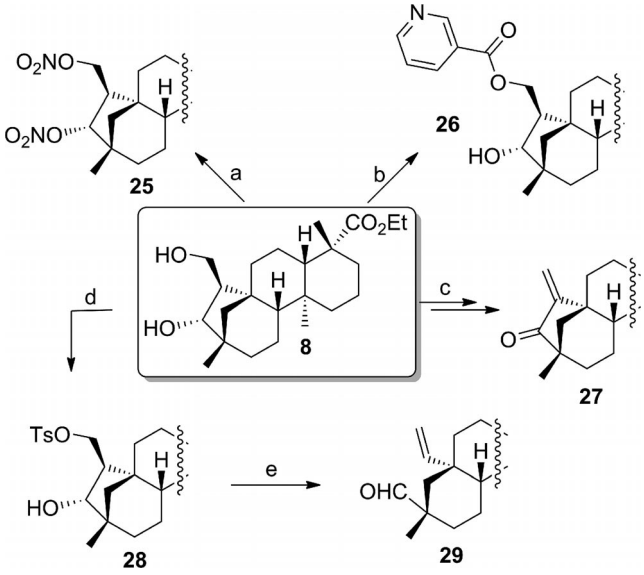
Compound **5** is converted into numerous aromatic esters **21** upon prior activation of the appropriately substituted benzoic acid with DCC/DMAP and reaction with **5** (R = Me).[29] Acetates **22** (R = H, Me) can be obtained by the reaction of **5** with excess acetic anhydride in pyridine.[30] Mannosylation following the Schmidt imidate protocol yields glycoside **23**.[31] Derivative **5** (R = Et) can also be transformed into acrylates **24a** and **24b** (Scheme 6). Upon DCC/DMAP activation of 1 equivalent of acrylic acid, reaction with **5** leads to the formation of **24a** in a yield of 85%, whereas the application of 2 equivalents of acrylic acid leads to the formation of **24b** in a yield of 75%.[10,11,14]

Diol **8** exhibits two hydroxy groups in close vicinity, defined stereochemistry and a sterically congested environment. Consequently, **8** [obtained in a one-pot reaction from (–)-isosteviol, Scheme 2] is a versatile and attractive precursor for subsequent functionalization (Scheme 7).

Reaction with nitric and sulfuric acid in dichloromethane yields the dinitrate **25** in 80% yield.[10,11] Treatment of **8** with 1 equivalent of nicotinoyl chloride and sodium carbonate[10] or triethylamine[11] leads to the ester **26** in a yield of 81% for both reactions. Likewise, with 2 equivalents of nicotinoyl chloride, the corresponding twice-esterified product can be obtained in a yield of 88%. α-Methylene ketone **27** can be synthesized through a series of transformations (Scheme 7).[14] First, the primary hydroxy function is regioselectively acylated with acetyl chloride. Subsequently, the secondary hydroxy function is oxidized to the corresponding ketone with pyridinium dichromate (PDC). In the last step, reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine under basic conditions gives product **27** in a β-elimination reaction. The oxidation of the secondary hydroxy moiety of **8** can be carried out even in the presence of the nonprotected primary hydroxy moiety when using pyridinium chlorochromate (PCC) as oxidant.[14] The tosylation of **8** under standard conditions leads to the formation of primary tosylated alcohol **28** (Scheme 7). Treatment of **28** with sodium hydroxide results in Grob fragmentation, yielding ring-opened product **29** in an excellent yield of 96%. The structural features were confirmed by X-ray crys-

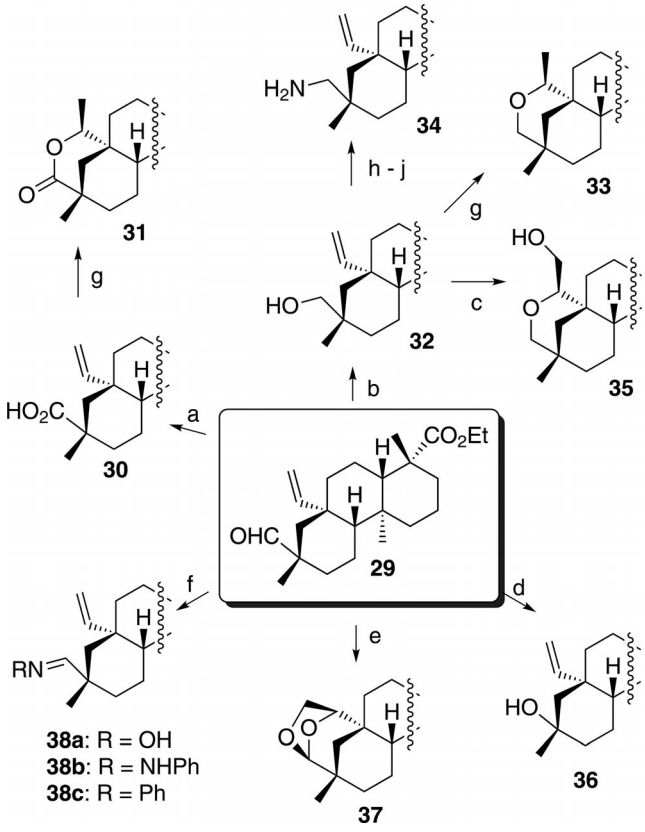


Scheme 6. Tranformations of alcohol **5**. Reagents and conditions: a) R = Me: DCC, DMAP, appropriately substituted benzoic acid, dioxane, reflux, 1 h, 68–72%; b) Ac_2O, pyridine, room temp., 2 d, 82% (R = H)/73% (R = Me); c) 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl trichloroacetamidate, $BF_3{\cdot}OEt_2$, 68% (R = Me); d) R = Et: DCC/DMAP, CH_2Cl_2, 1 equiv. acrylic acid, room temp., 12 h, 85% (**24a**)/2 equiv. acrylic acid, room temp., 16 h, 75% (**24b**).



Scheme 7. Tranformations of diol **8**. Reagents and conditions: a) HNO_3/H_2SO_4, CH_2Cl_2, 3 h, room temp., 80%; b) 1 equiv. nicotinoyl chloride, Na_2CO_3, $CHCl_3$, 1 h, 60 °C, 81%; c) i. MeCOCl, NEt_3, toluene, 2 h, room temp., 96%; ii. PDC, CH_2Cl_2, 3 h, room temp., 91%; iii. DBU, pyridine, 6 h, 80 °C, 85%; d) *p*TsCl, pyridine, 18 h, room temp., 75%; e) NaOH, CH_3CN, 3 h, room temp., 96%.

tallographic analysis.[11] Aldehyde **29** itself acts as a versatile starting material for a series of chemical transformations (Scheme 8).[10,11] Oxidation of the aldehyde moiety of **29** with Jones' reagent (CrO_3/8 N H_2SO_4 in acetone) gives carboxylic acid **30**, which can be cyclized to form δ-lactone **31** on treatment with $BF_3{\cdot}OEt_2$ in dichloromethane with the newly formed methyl moiety pointing upwards (β-orientation). The reduction of **29** with sodium borohydride in ethanol renders alcohol **32**. This substrate can also be cyclized under the same reaction conditions as applied to the carboxylic acid **30** to give the corresponding tetrahydropyran **33**.



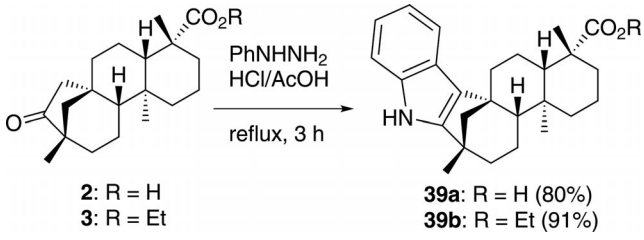
Scheme 8. Transformations of **29**. Reagents and conditions: a) Jones' reagent (8 N), acetone, 2 h, 0 °C, 90%; b) $NaBH_4$, EtOH, 10 min, 0 °C, 96%; c) *m*CPBA, CH_2Cl_2, 5 h, 0 °C, 78%; d) MeOH, NaOH, H_2O_2, 4 h, 65 °C, 75%; e) $NaIO_4$, NaBr, AcOH, 3 h, 90 °C, 84%; f) R = OH: $HONH_3Cl$, $NaHCO_3$, EtOH, 2 h, 60 °C, 97%/R = NHPh: EtOH, $PhNHNH_2$, 3 h, 10 °C, 95%/R = Ph: aniline, CH_2Cl_2, 3 h, 40 °C, 84%; g) $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux, 30 h, 74% (for **31**), 75% (for **33**); h) *p*TsCl, pyridine, room temp., 12 h, 85%; i) NaN_3, DMF, 80 °C, 3 h, 80%; j) PPh_3, H_2O, 65 °C, 3 h, 85%.

Tosylation of the alcohol moiety of **32** leads to azide formation and subsequent reduction of the azide moiety gives the amine analogue **34**.[10,11] Despite the neopentyl nature of the products, the yields seem to be remarkably good. Epoxidation of the double bond in **32** with *m*CPBA leads to the intermediate epoxide, which undergoes cyclization to give hydroxymethyl derivative **35**. Baeyer–Villiger oxidation of **29** with hydrogen peroxide under basic conditions gives an intermediate formate. Subsequent hydrolysis or decarbonylation leads to alcohol **36** (Scheme 8).[11] Moreover, the double bond in **29** can be dihydroxylated with sodium periodate and the intermediate diol then is able to undergo

ring closure.[10] Acetal **37** is thus obtained in a yield of 84%; the relative configuration was confirmed by X-ray diffraction analysis. The oxime derivative **38a** can be synthesized in analogy to (–)-isosteviol by employing hydroxylamine hydrochloride. Upon slight heating in sulfuric acid, dehydration occurs to yield the corresponding nitrile derivative. Aromatic hydrazones **38b** can be accessed by converting aldehyde **29** using the appropriate aromatic hydrazine substrates. Thus, phenylhydrazine as well as 4-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine have been employed to give the corresponding hydrazones in yields of 95, 85, and 81%, respectively.[10] Imine **38c** can be obtained by treating **29** with aniline (or derivatives thereof). Reduction with sodium borohydride also results in the formation of the appropriate secondary amine.[10] Information about the newly formed stereochemistry was not provided.

2.2. Heterocyclic Derivatives

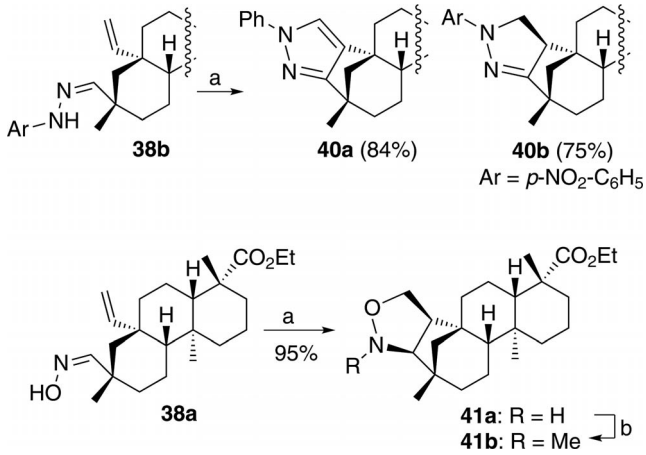
Several heterocyclic compounds can be synthesized from the isosteviol derivatives described above. Starting from (–)-isosteviol (**2**; R = H) or its ethyl ester **3** (R = Et), indoles **39** can be synthesized (Scheme 9).[10] Condensation with phenylhydrazine leads to the formation of the hydrazone derivative, which directly undergoes a Fischer indole reaction to yield **39**.



Scheme 9. Indoles derived from (–)-isosteviol.

$BF_3{\cdot}OEt_2$-induced cyclization between the hydrazone moiety and the vinyl group in **38b** (Scheme 10, Ar = Ph) renders the aromatic pyrazole derivative **40a**. Interestingly, when subjecting the analogous *p*-nitrophenyl hydrazone (Ar = *p*-$NO_2C_6H_5$) to the same reaction conditions, the 4,5-dihydro-1*H*-pyrazole **40b** was obtained. However, treatment of the 2,4-dinitrophenyl hydrazone did not lead to any cyclization product as the two electron-withdrawing groups prevent Lewis-acid-catalyzed cycloaddition. It was found instead that treatment with $BF_3{\cdot}OEt_2$ leads to reduction of the C=C double bond in **38b** to give a minimum yield of 84%.[11]

A mechanistic rationale for the hydrogenation of the vinyl moiety is not given and difficult to comprehend. Treatment of the analogous oxime **38a** (Scheme 10) with $BF_3{\cdot}OEt_2$ also leads to a 1,3-dipolar cyclized product, which originates from the tautomeric nitrone. Thus, isoxazolidine **41a** was obtained in excellent yield. This derivative can also be modified at the nitrogen atom. Reaction with, for example, iodomethane and NaH in DMF renders methylated product **41b** in a quite attractive yield of 85%.



Scheme 10. Pyrazoles and isoxazolidines derived from (–)-isosteviol. Reagents and conditions: a) $BF_3{\cdot}OEt_2$, toluene, 2 h, 118 °C; b) MeI, NaH, DMF, 50 °C, 2 h, 85%.

The stereochemical features of **41a** were confirmed by NOESY experiments.[10,11]

2.3. Biological Profile of the Presented Compounds

A large number of the derivatives described so far were tested for their biological activities. Table 1 displays a selection of those compounds that exhibit enhanced biological activity. The biological activities evaluated included the inhibition of α-glucosidase,[14] *M. tuberculosis* growth[23,24] as well as seed germination and root elongation.[29] Furthermore, the cytotoxic activity against B16-F10 melanoma cells,[11] *staphylococcus aureus* and *bacillus subtilis*,[10] were also studied.

Several structure–activity relationships can be observed when analyzing these results. First, derivatives displaying one or more hydroxy moieties exhibit much higher activities than (–)-isosteviol itself. The activity increases with the number of hydroxy groups. This might be attributed to better bioavailability. Secondly, it was found that the carboxylic acid derivatives show lower bioactivity than the corresponding esters. Thirdly, the introduction of amine, oxime, or heterocyclic moieties into the (–)-isosteviol architecture further enhances their cytotoxic activities. In addition to the substrates listed below with enhanced biological activities, a huge number of other (–)-isosteviol derivatives show only moderate biological activities upon screening for their cytotoxic potential.[10,14]

2.4. Reactions at the Carboxylic Acid

Aside from standard esterification reactions, which can be applied to any carboxylic acid, the number of reported possible modifications at the 19-position of (–)-isosteviol is relatively limited. Reduction of the carboxylic acid and, at the same time, the keto moiety can be carried out with lithium aluminium hydride.[32] Various amino acid amides **42a**–**42e** (Figure 3) of (–)-isosteviol were synthesized upon DCC

Table 1. (–)-Isosteviol derivatives exhibiting enhanced biological activities.

	Biological activity	Inhibition activity
5	α-Glucosidase	IC_{50} = 132.1 μM (R = Et) IC_{50} = 156.3 μM (R = H)
	B16-F10 melanoma cells	IC_{50} = 58 μM (R = Et)
8	α-Glucosidase	IC_{50} = 86.2 μM (R = Et) IC_{50} = 148.6 μM (R = H)
	B16-F10 melanoma cells	IC_{50} = 68 μM (R = Et)
	Staphylococcus aureus	66% (R = Et)[a]
9	α-Glucosidase	IC_{50} = 88.9 μM (R = Et) IC_{50} = 92.1 μM (R = H)
10	*M. tuberculosis*	MIC = 10–20 μg/mL[b]
12a	α-Glucosidase	IC_{50} = 91.2 μM (R = Et) IC_{50} ≥ 200 μM (R = H)
12b	α-Glucosidase	IC_{50} = 113.6 μM (R = Et)
21a, **21b**, **21c**	Seed germination	43–69%[b]
21b, **21c**, **21d**	Root elongation	44–78%[c]
24a	*Staphylococcus aureus*	84% (R = Et)[a]
24b	*Staphylococcus aureus*	77% (R = Et)[a]
25	*Bacillus subtilis*	MIC = 12.5 μg/mL[d]
	Staphylococcus aureus	75%[a]
26	B16-F10 melanoma cells	IC_{50} = 25 μM
	Bacillus subtilis	MIC = 12.5 μg/mL[d]
	Staphylococcus aureus	32%[a]
30	*Bacillus subtilis*	MIC = 12.5 μg/mL[d]
	Staphylococcus aureus	63%[a]
32	B16-F10 melanoma cells	IC_{50} = 24 μM
	Bacillus subtilis	MIC = 6.25 μg/mL[d]
	Staphylococcus aureus	59%[a]
35	*Bacillus subtilis*	MIC = 6.25 μg/mL[d]
	Staphylococcus aureus	71%[a]
36	B16-F10 melanoma cells	IC_{50} = 26 μM
	Bacillus subtilis	MIC = 12.5 μg/mL[d]
38a	B16-F10 melanoma cells	IC_{50} = 27.5 μM
	Bacillus subtilis	MIC = 1.56 μg/mL[d]
	Staphylococcus aureus	40%[a]
39	α-Glucosidase	IC_{50} = 68.2 μM (R = Et) IC_{50} = 83.2 μM (R = H)
40a	B16-F10 melanoma cells	IC_{50} = 19 μM
40b	B16-F10 melanoma cells	IC_{50} = 21 μM
41a	B16-F10 melanoma cells	IC_{50} = 15 μM

[a] Inhibition [%] determined at a concentration of 100 μg/mL of the compound. [b] Inhibition [%] of seed germination. [c] Inhibition [%] of root elongation. [d] MIC = minimum inhibition concentration.

activation and coupling with the corresponding amino acid methyl esters,[29] some of which show inhibitory effects on seed germination or root elongation.

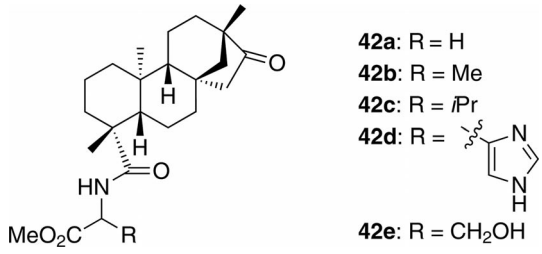
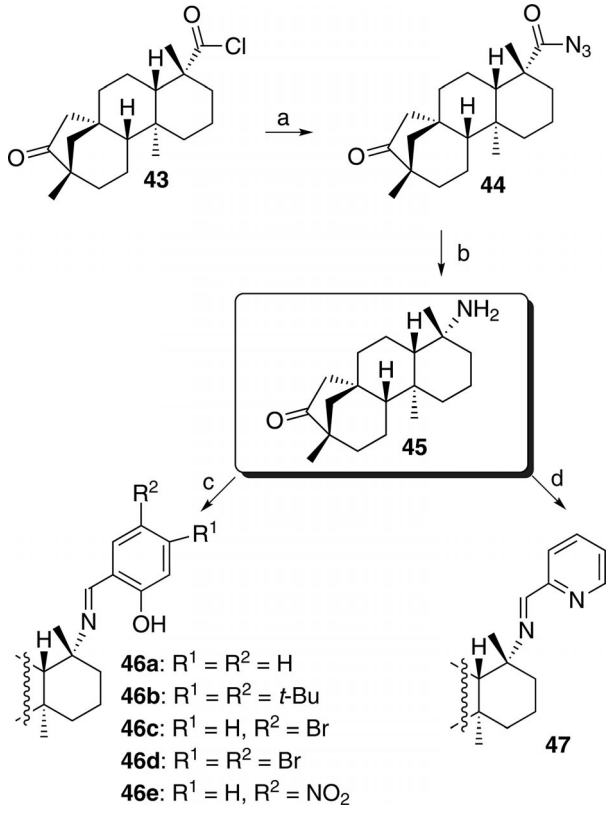


Figure 3. Amino acids **42a**–**42e** modified with (–)-isosteviol.

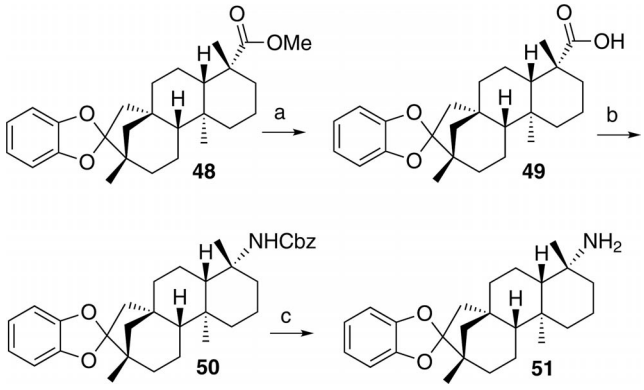
In a Curtius-type rearrangement, the carboxylic acid moiety of **2** can be stereospecifically converted into the corresponding amine **45** (Scheme 11).[26] Activation of the acid with thionyl chloride[33] or phosphorus trichloride[34] to give **43** and subsequent reaction with sodium azide renders the acyl azide derivative **44**. Upon heating in benzene at reflux, Curtius rearrangement occurs to give the intermediate isocyanate. Amine **45** can then be obtained directly as the hydrochloride from the isocyanate by acid hydrolysis.[26] Compound **45** can function as the starting compound for the synthesis of a variety of Schiff bases. Reaction of the amine with appropriately substituted aldehydes leads to the formation of derivatives **46a**–**46e** and **47**. Despite the steric demand of the primary amine **45**, the yields of the imines are astonishingly good. The potential applications of these Schiff bases as ligands for metal complex catalysis could not be realized, however, due to the formation of insufficient quantities of complexes with, for example, vanadium acetylacetonate.[26]



Scheme 11. Formation of the amine of (–)-isosteviol and conversion to Schiff base derivatives. Reagents and conditions: a) NaN_3, acetone, 15 min, room temp., 70%; b) 1. benzene, reflux, 6 h, 86%; 2. benzene, conc. HCl, 6 h, 55%; c) ArCHO, benzene, 2 h, reflux 83–93%; d) pyridine-2-carbaldehyde, benzene, 1 h, reflux, 74%.

By employing a similar reaction procedure to that in Scheme 11, the amine **51** of the (–)-isosteviol catechol ketal was synthesized by Waldvogel and co-workers in the course of their studies directed towards the construction of triphenylene ketals (Scheme 12).[35] As a result of the high steric demand surrounding the ester moiety of catechol ketal **48**, it was first demethylated by using sodium cyanide to provide carboxylic acid **49**. After activation of the carboxylic acid by using Vilsmeyer′s reagent, the corresponding acyl azide was formed upon reaction with sodium azide. Direct activation by using azide transfer reagents[36,37] like

diphenylphosphoryl azide (DPPA)[38] did not give sufficient conversions because the environment of the carboxylic acid is sterically too congested.



Scheme 12. Formation of the amine **51** of the (–)-isosteviol catechol ketal. Reagents and conditions: a) NaCN, DMF, reflux, 24 h, 88%; b) 1. oxalyl chloride, DMF, CH_2Cl_2; 2. pyridine, THF, NaN_3, room temp., 16 h; 3. toluene, BnOH, NEt_3, reflux, 48 h, 89%; c) $Pd(OH)_2$/C, H_2, THF, 98% (see the Supporting Information).

Upon heating in toluene at reflux, Curtius rearrangement occurs to give the isocyanate. Trapping of the isocyanate with benzylic alcohol leads to the formation of the Cbz-protected amine **50**, which can then be liberated under reductive conditions by reaction with Pearlman's catalyst under hydrogen to yield amine **51**.

2.5. Microbial Hydroxylations

The treatment of organic substrates by microorganisms often opens up the possibility of positions being attacked that are usually not prone to conventional transformations in organic chemistry. Alongside a variety of structurally related diterpenes,[39] (–)-isosteviol (**2**) can be transformed by a variety of microorganisms to yield mainly hydroxylated derivatives (Figure 4). Microbial oxidation of a total of eight positions (highlighted in grey, Figure 5) of the *ent*-beyerane skeleton has been achieved so far. Upon feeding (–)-isosteviol to the mutant B1-41a of *Gibberella fujikuroi*, a fungal plant pathogen, hydroxylation of the 6- and 7-positions was achieved.[40] By transforming isosteviol with *Gibberella fujikuroi* (also known as *Fusarium verticilloides*) itself, modification of the 12-position was accomplished.[41] Biotransformation with other fungi leads to hydroxylation reactions at the 1- and/or 7-positions (*Aspergillus niger*/*Rhizopus arrhizus*) as well as the 17-position (*Penicillium chrysogenum*).[42] Metabolization of isosteviol with bacteria of *Actinoplanes sp.* also allows hydroxylation at the 11-postion as well as at the 12- and 17-positions, whereas metabolization under the influence of *Mucor recurvatus* or *Cunninghamella blakesleeana* affords hydroxylation at the 15- and 9-positions, respectively.[43] Microbial hydroxylation of a methyl group other than that at the 17-position has not been reported so far.

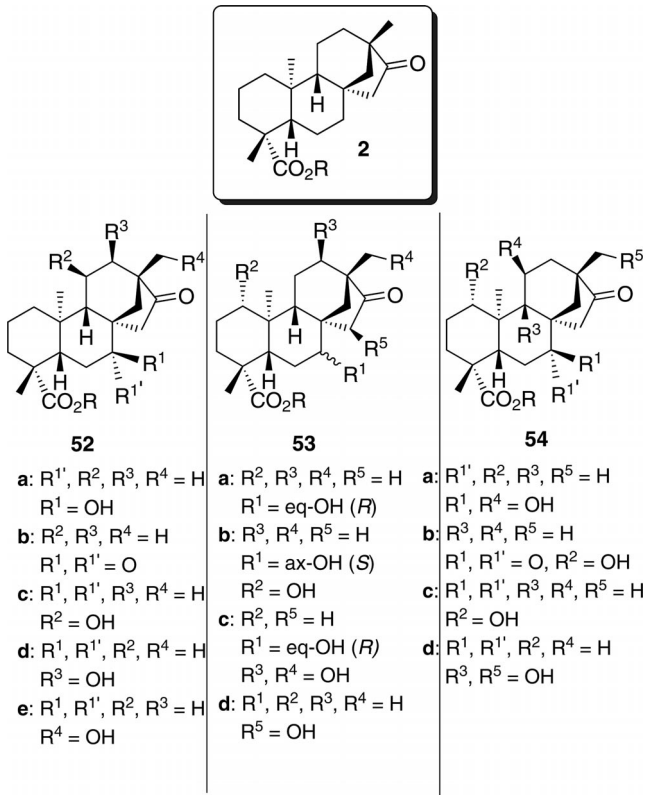


Figure 4. Microbial hydroxylation reactions of (–)-isosteviol.

A large number of the hydroxylated products also exhibit enhanced biological activity compared with (–)-isosteviol itself. Thus, compounds **52a**–**52e** (Figure 4) show an increased inhibitory effect on the Epstein–Barr virus activation, a human herpes virus that is associated with various kinds of cancer.[44] Hydroxylated products **53a**–**53d** exhibit activities as potential androgen agonists in the treatment of androgen insufficiency, showing even higher activity than testosterone. Furthermore, compounds **54a**–**54d** show anti-inflammatory properties.[45] Moreover, **52a** and **53b** inhibit AP-1 activation, AP-1 being a protein that is associated with, for example, the growth of breast cancer.[46]

Some of the derivatives of (–)-isosteviol have also been subjected to microbial transformations (Figure 5). (–)-Isosteviol can be transformed into the regioisomeric lactones **55** and **58** by the Baeyer–Villiger reaction. The regioisomers can be separated by column chromatography.[47] The introduction of hydroxy moieties at a total of six positions (highlighted in grey) in **55** has previously been reported.[47,48] Of the reported substrates, **56a**–**56e** have been shown to inhibit AP-1 activation. The three derivatives **58a**–**58c** of the regioisomeric lactone show inhibitory effects against AP-1 activation (**58a** and **58b**)[48] as well as androgen insufficiency (**58c**).[47]

Furthermore, oxime **9c** and nitriles **59** and **60a** act as AP-1 agonists whereas oxime **9b** and lactam **57a** show inhibitory effects against NF-κB, a transcription factor, the activation of which is associated with inflammatory processes.[49] Recent studies have also revealed that oxime **9a**,

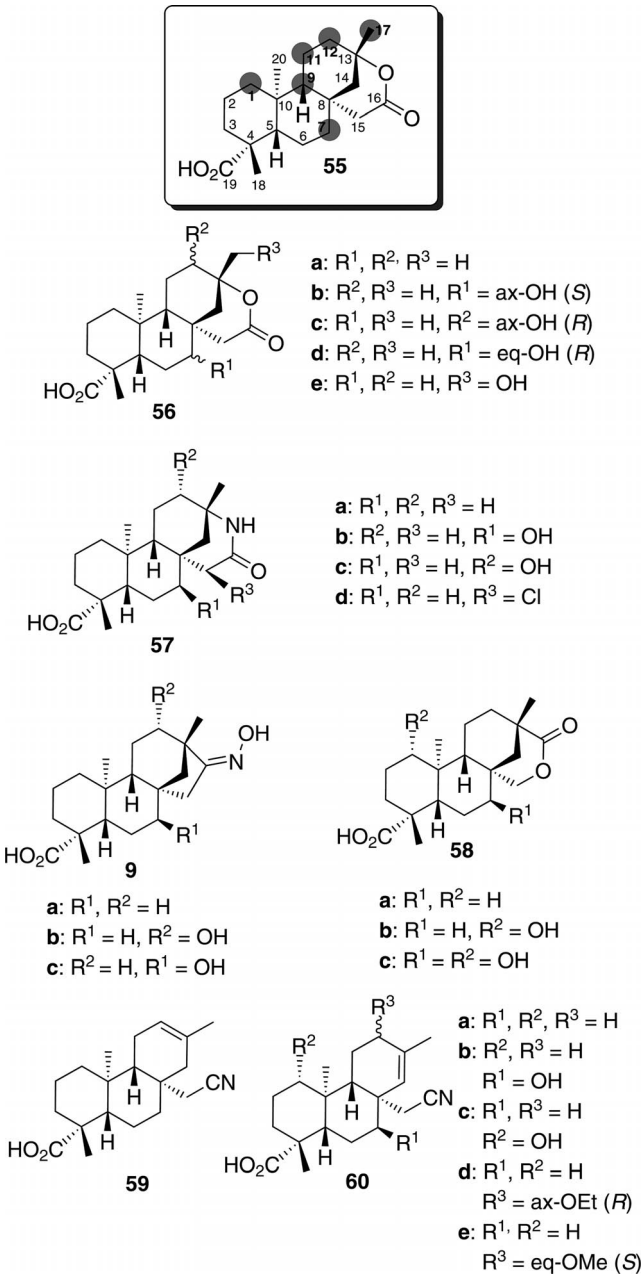


Figure 5. Microbial hydroxylations of (–)-isosteviol derivatives.

lactams **57a**–**57d**, and nitriles **60a**–**60e**, obtained by microbial transformation with *Absidia pseudocylindrospora* and *Aspergillus niger*, exhibit suppressive effects on iNOS (induced nitric oxide synthase) expression, which plays a crucial role in inflammatory processes.[50] Hydroxylation at the 6- and 7-positions of dihydroisosteviol **5** (Scheme 6) has been reported by de Oliveira et al.[51]

2.6. Derivatives with an Expanded Ring D

Although a huge number of derivatives of (–)-isosteviol are known, only a very limited number of these exhibit different sizes of the D ring. Six-membered ring lactones **56a** (R, R′ = H) and **58a** (R, R′ = H) can be synthesized by Baeyer–Villiger reaction starting from (–)-isosteviol (Figure 6).[47,52] Through a series of subsequent modifications, **56a** can, for example, be transformed into the novel neuroprotective substances serofendic acids A and B.[53] Lactone derivative **56f** (R = Bn), with the hydroxymethylene moiety located in the axial position, can be obtained by subjecting the appropriately substituted benzylic ester of (–)-isosteviol to Baeyer–Villiger reaction conditions.[54] This compound can be converted into methylene derivative **56g** after tosylation and subsequent elimination of the hydroxy moiety. The methylene double bond in **56g** also undergoes epoxidation when treated with *m*CPBA. Lactone **31** and tetrahydropyran **33** (Figure 6) can be obtained upon treatment of **30** and **32** (Scheme 8), respectively, with $BF_3{\cdot}OEt_2$.

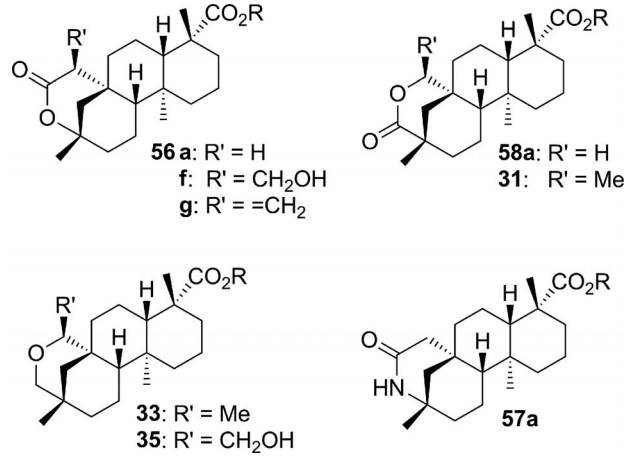
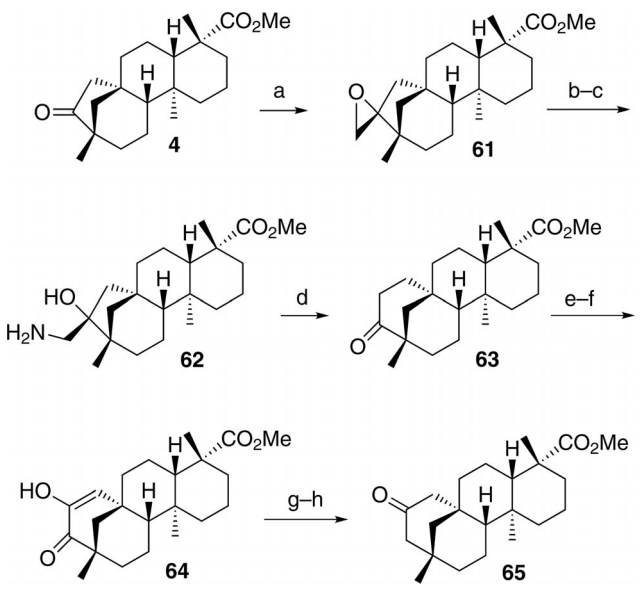


Figure 6. Heterocyclic derivatives of (–)-isosteviol with an expanded ring D.

The analogous lactam **57a** (Figure 6) can be obtained by conversion of oxime derivative **9** (R = H, Et) under acidic conditions.[14] It was found that, depending on the reaction conditions, Beckmann fragmentation of the oxime occurs alongside the Beckmann rearrangement. Thus, nitrile components **59** and **60a** (Figure 5) were also obtained.[6] When employing $BF_3{\cdot}OEt_2$ in the reaction, the ratio of lactam to nitriles is around 3.5:1 (77 vs. 22%). Upon switching to sulfuric acid, the ratio changes to about 1:14 (6% vs. 88%) in favor of the nitrile products. Reaction with *p*-toluenesulfonic acid renders a mixture with a ratio of about 1.4:1 (55% vs. 38%) in favor of the lactam.

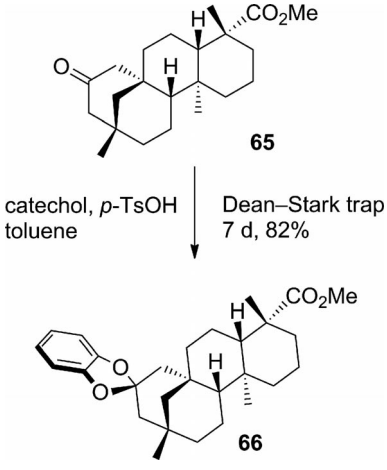
In 2012, Waldvogel and co-workers were the first to report the ring enlargement of the (–)-isosteviol D ring to a six-membered ring containing exclusively carbon atoms.[55] Corey–Chaykovsky epoxidation[56] of **4** provides epoxide **61** as a single isomer (Scheme 13). After ring-opening of **61** with sodium azide and subsequent reduction, the corresponding amine **62** was then converted in a Tiffeneau–Demjanov-type rearrangement.[57] Surprisingly, migration of the lower substituted alkyl fragment occurred, leading to the formation of cyclohexanone derivative **63** in an overall yield of 67% starting from **61**. With the aim of synthesizing novel building blocks for the construction of triphenylene ketals, the keto function in **63** was then translocated in a

series of redox reactions to yield ketone **65**. The reaction sequence includes the bromination of **63** at the position α to the keto function[58] and subsequent oxidation under strongly basic conditions to give the keto enol **64**. Reduction of the keto function followed by deoxygenation of the newly formed hydroxy group using trimethyliodosilane[59] finally gave **65** in an overall yield of 16% starting from **4**.



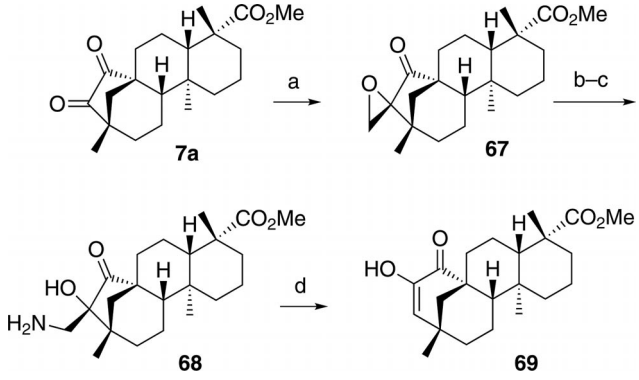
Scheme 13. Ring enlargement of (–)-isosteviol and shift of the keto function. Reagents and conditions: a) SMe_3I, KO*t*Bu, DMF, 0 °C, 1 h, room temp., 3 h, 88%; b) NaN_3, DMF, 10 d, 90 °C; c) Pd/C, H_2, THF, 4 d, room temp.; d) HOAc, $NaNO_2$, 30 min, 0 °C, 3 h, room temp., 67% (three steps starting from **61**); e) NBS, *p*TsOH, 20 min, 145 °C, 83%; f) NaOH, DMF, 5 h, room temp., 69%; g) $NaBH_4$, MeOH, 0 °C, 1 h, room temp., 2 h, 81%; h) TMSI, CH_2Cl_2, room temp., 8 h, 58%.

Derivative **65** was then subjected to ketalization with catechol to yield acetal **66** in good yield (Scheme 14). The application of this strategy to the construction of supramolecular receptors is the subject of current work.



Scheme 14. Ketalization of **65** (see the Supporting Information).

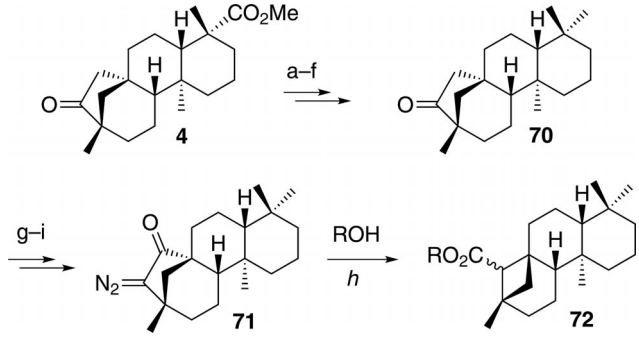
The synthesis of regioisomeric keto enol **69** (Scheme 15) was achieved by following the reaction strategy described above for the conversion of **4**, the only difference being that the synthesis starts with the (–)-isosteviol diketone **7a**. Epoxidation under Corey–Chaykovsky conditions with 1 equivalent of SMe_3I regioselectively converts the less hindered keto function to yield epoxide **67**.



Scheme 15. Ring enlargement of (–)-isosteviol diketone **7a** renders keto enol **69**. Reagents and conditions: a) 1 equiv. SMe_3I, KO*t*Bu, DMF, 0 °C, 1 h, room temp., 3 h, 90%; b) NaN_3, DMF, 2 d, 80 °C; c) Pd/C, H_2, THF, 2 d, room temp.; d) HOAc, $NaNO_2$, 30 min, 0 °C, 3 h, room temp., 13% (three steps starting from **67**).

The use of 2 equivalents of SMe_3I gives the corresponding twice-epoxidized product. Again, ring-opening with sodium azide and reduction leads to the formation of amine **68**, which was subjected to rearrangement under Tiffeneau–Demjanov conditions to yield keto enol **69**.

In addition to these ring-enlargement transformations, the contraction of ring D from five to four carbon atoms in a multiple-step synthesis has been reported (Scheme 16).[19] Starting from (–)-isosteviol methyl ester **4**, the ester functionality was, after protection of the keto function, removed reductively to yield the *ent*-beyerane scaffold **70**.



Scheme 16. Ring contraction of (–)-isosteviol derivatives. Reagents and conditions: a) 2,2-Dimethylpropane-1,3-diol, *p*TsOH, benzene, 32 h, reflux; b) $LiAlH_4$, Et_2O, 2 h, room temp., 78% (two steps); c) $MeSO_2Cl$, NEt_3, pentane, 2 h; d) PhSNa, DMF, 110 °C, 16 h; e) Li/NH_3, THF, –33 °C, 3 h; f) *p*TsOH, dioxane, H_2O, room temp., 24 h, 64% (four steps); g) SeO_2, xylene, reflux, 42 h, 85%; h) $TsNHNH_2$, $CHCl_3$, room temp., 30 h, quant.; i) Al_2O_3, CH_2Cl_2, room temp., 62 h, 79%.

Riley oxidation to the corresponding diketone and subsequent reaction with *p*-tosylhydrazine and aluminium oxide leads to the formation of diazo compound **71**. Irradiation with a mercury lamp in the presence of water (R = H) or methanol (R = Me) finally yields ring-contracted product **72** by a Wolff rearrangement as a mixture of isomers.

3. Applications

In addition to the testing of (–)-isosteviol and its derivatives in medicinal chemistry, this unique molecular architecture has found applications in various fields of organic chemistry as a result of its superb structural features. Significant work has been carried out in supramolecular chemistry and organocatalysis.

3.1. Supramolecular Chemistry

As a result of the rigid, "chemically inert" hydrocarbon backbone of (–)-isosteviol and the two functional groups arranged in a concave fashion, this naturally derived and optically pure compound exhibits two fundamental structural features that can be used in supramolecular chemistry. First, the rigid nature of the diterpenoid skeleton limits the degrees of freedom and, secondly, ensures excellent preorganization of the molecules.[60] Modification of either or both functional groups also allows the synthesis of a variety of derivatives with the exact characteristics that are desired for a specific system.

(–)-Isosteviol itself shows qualities suited to supramolecular interactions with other molecules. Thus, (–)-isosteviol forms chiral complexes with aromatic compounds such as aniline or toluene.[61] These complexes are stabilized through hydrogen bonding between the isosteviol molecules themselves as well as by hydrogen bonds between isosteviol and, for example, the amine moiety of aniline. In the solid state, these interactions lead to the formation of chiral double helices. The helical strands are composed of isosteviol molecules, and the strands themselves are linked to each other through hydrogen bonding to the aniline molecules. Furthermore, each helix is linked to a neighboring helix, again through hydrogen bonds.

Tweezer-like structures such as **73** and **74** can be formed by linking two (–)-isosteviol molecules to spacers (Figure 7). Both the keto and carboxylic acid moieties can be used to form the linkage. Stereoselective reduction of the keto moiety of (–)-isosteviol with, for example, sodium borohydride[10,62] and subsequent reaction with aliphatic acid chlorides leads to the formation of dicarboxy derivative **73**, linked by various (poly)methylene spacers.[63] These substrates exhibit moderate tuberculostatic activities, depending on the chain length.[62] Furthermore, they proved capable of transporting Fe^{III} picrates through a liquid chloroform membrane, which functions as a model of a cell membrane.[64]

Upon activation of the carboxylic acid of (–)-isosteviol as the acid chloride and subsequent reaction with, for example, diols,[65] dibromoalkanes,[66] or diamines, tweezer-like structure **74** can be obtained.[67,68] These diamide structures have proven to be potent receptors and carriers of amino acid picrates based on phenylalanine and tryptophan through a liquid chloroform phase,[67] partly exhibiting better extraction ability than dibenzo-18-crown-6. In addition to the methylene or amide spacers depicted in Figure 7, azine and hydrazide linkers[69] (showing high tuberculostatic activity) as well as aliphatic amide linkers[67,68] have been reported. Moreover, the anhydride of (–)-isosteviol can be obtained by treating (–)-isosteviol with isostevioyl chloride.[33]

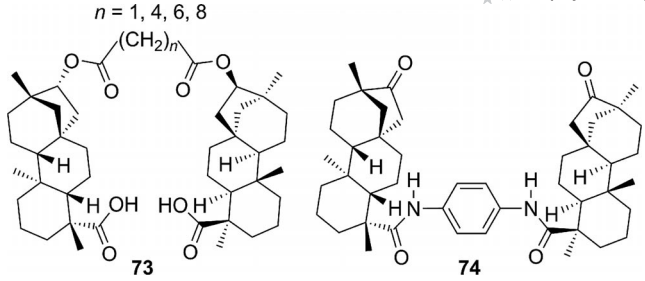


Figure 7. Tweezer-like structures based on (–)-isosteviol.

Macrocyclic compounds have attracted particular interest in recent years due to their ability to act as host molecules in supramolecular recognition processes. Various kinds of macrocycles have been synthesized based upon (–)-isosteviol. For example, based upon the tweezer-like structure **73** (Figure 7), closely related macrocycle **75** (Figure 8) can be obtained by two-fold esterification with 1,3-propanediol and malonyl chloride.[70] It was found that **75** exhibits enhanced tuberculostatic activity, inhibiting the in vitro growth of *Mycobacterium tuberculosis*.

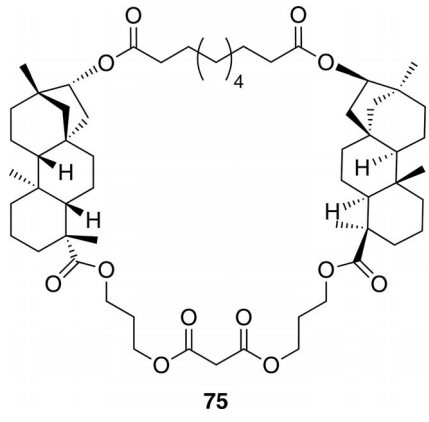


Figure 8. Isosteviol-based macrocycle **75**.

Reduction of both the keto and carboxylic acid moieties of (–)-isosteviol to the corresponding alcohols at the same time and subsequent reaction with, for example, aliphatic dicarboxylic acids renders macrocycles that are structurally similar to tweezer structure **73** and macrocycle **75**.[32] Unfortunately, these macrocyclic structures have been little characterized.

The two biologically active molecules isosteviol and chlorin E6 were combined in the synthesis of macrocycle **76** and similar structures with enhanced biological properties (Figure 9).[71] In a multistep sequence that includes amide and oxime formation as well as esterification, bicyclic macrocycle **76** was obtained in an overall yield of less than 16%. However, its possible application in medicinal chemistry and an evaluation of its biological activities have not yet been reported.

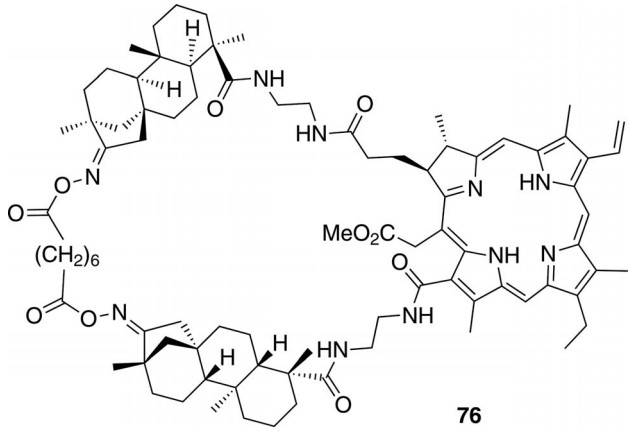
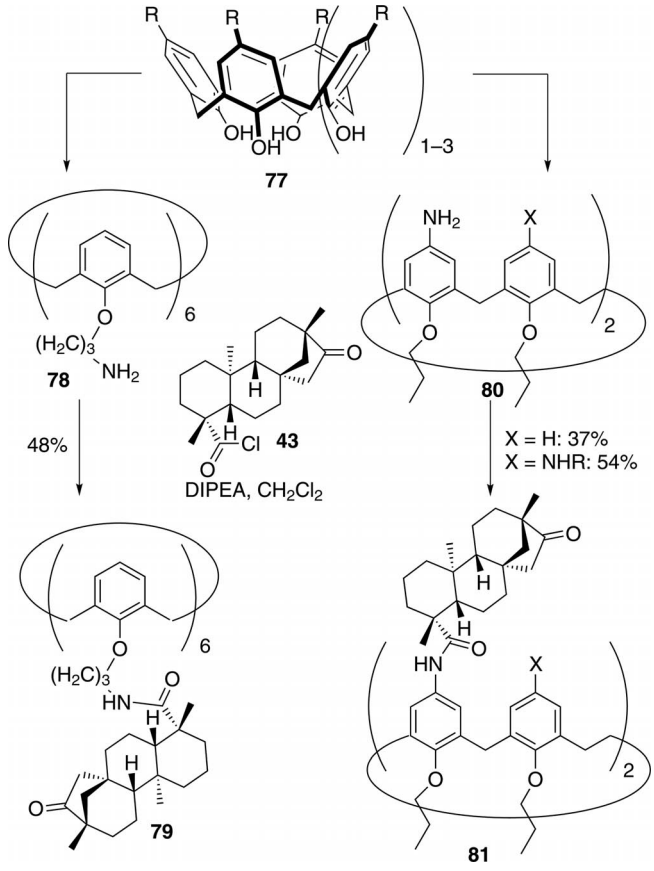


Figure 9. Isosteviol–chlorin macrocycle **76**.

Calixarenes **77** (Scheme 17) have found widespread application in organic chemistry as receptor scaffolds for various types of molecules.[72] Calixarenes can be easily functionalized at the upper and lower rims. Thus, receptors capable of forming supramolecular interactions with anions as well as cations or neutral molecules can be accessed. Isostevioyl chloride **43** can be obtained by conversion of (–)-isosteviol with, for example, thionyl chloride. Reaction of **43** with hexaaminocalix[6]arene **78** under basic conditions leads to the functionalization of the lower rim of the calixarene and the formation of compound **79** (Scheme 17).[73] Likewise, the reaction of calix[4]arene **80** with isostevioyl chloride leads to modification of the upper rim to yield compound **81**.

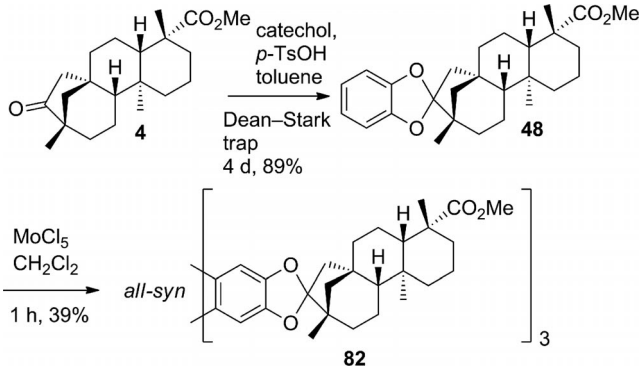
A single signal for the benzylic methylene protons in the ^{1}H NMR spectrum of compound **79** indicates rapid interconversion of the macrocycle between different conformers, whereas the presence of two defined doublets for the corresponding protons in the ^{1}H NMR spectrum of **81** indicate a cone conformation of **81** with defined equatorial and axial positions. These substrates were synthesized with the prospect of achieving a recognition system for saccharides and organic anions, as well as the formation of artificial ion channels. Studies on this topic are currently being investigated by Al'fonsov and co-workers.

Over the past few years, Waldvogel and co-workers have employed triphenylene ketal based receptor structures in the molecular recognition and detection of various aromatic compounds like caffeine.[37,74,75] Further modification of the binding sites of the host scaffold with optically active entities provides an opportunity for achieving enantiofacial differentiation of the bound guest molecule.[76] Unfortu-



Scheme 17. Synthesis of calixarenes based on (–)-isosteviol.

nately, the applied (–)-menthylamine building blocks[77] completely shield the supramolecularly oriented guest preventing its application in catalysis.[36] By using the optically active (–)-isosteviol as backbone building block in the synthesis of such receptor structures, subsequent chiral modification steps can be avoided. After methylation of (–)-isosteviol, ester derivative **4** can be converted into the corresponding catechol ketal **48** (Scheme 18).[35]



Scheme 18. Ketalization and subsequent oxidative trimerization of **4**.

Oxidative trimerization of **48** renders receptor scaffold **82** as a mixture of isomers (*all-syn* and *anti*,*anti*,*syn*). Separation of the isomers can be achieved by column chromatography, and the *all-syn*-ester **82** was isolated in a yield of

39%. This is a higher yield than statistics would predict. The formation of a template due to the molybdenum salts can be assumed.[78] The three-dimensional structure was elucidated by X-ray analysis (Figure 10), showing the planar triphenylene platform and the cavity formed by the (–)-isosteviol backbone.[35]

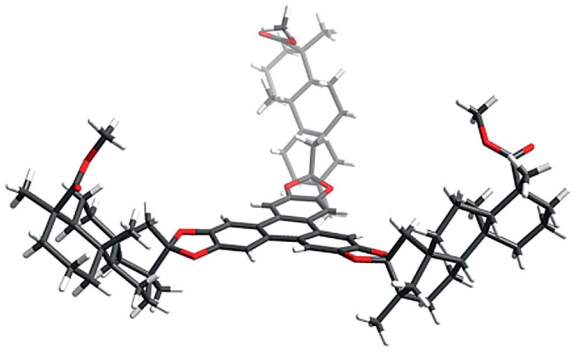
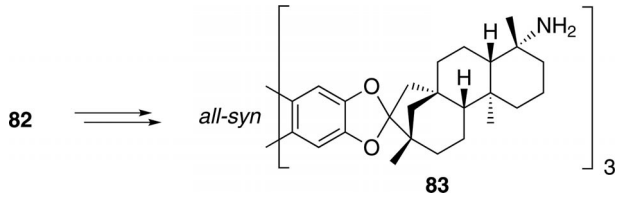


Figure 10. Molecular structure of **82** obtained by X-ray analysis.

The binding of a substrate (for example, electron-deficient heterocyclic compounds) in this kind of host molecule occurs through π–π interactions with the electron-rich triphenylene platform and, more importantly, through hydrogen-bonding interactions with the binding sites of the receptor.[37,74] Over a series of steps that include demethylation, azide formation, and Curtius rearrangement, **82** can be transformed into the corresponding triamine **83** (Scheme 19).[35]



Scheme 19. Receptor scaffold based on (–)-isosteviol.

all-syn-Triamine **83** can be further modified by introducing suitable binding sites that might be capable of forming hydrogen-bonding interactions with an intercalated guest molecule.

3.2. Organocatalysis

Because (–)-isosteviol is a readily available ex-chiral-pool building block, it has become an attractive substrate as a chiral auxiliary in organocatalytic chemistry. In combination with amino acids such as proline, conjugates like **84** can be formed (Figure 11) that exhibit amphiphilic properties, thereby allowing reactions of organic compounds to be performed in aqueous media. This presents a highly environmentally friendly alternative for a variety of stereoselective conversions that, so far, had been carried out exclusively in organic solvents.

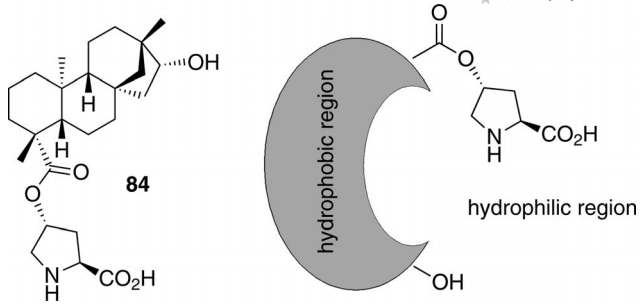
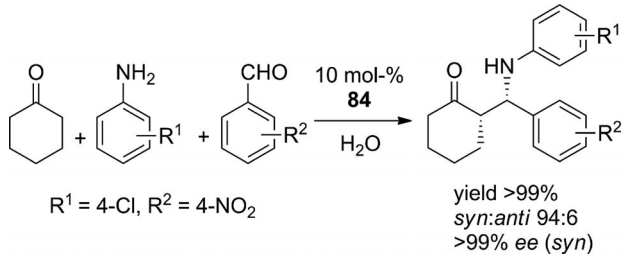


Figure 11. Amphiphilic (–)-isosteviol-proline conjugate **84**.

This kind of amphiphilic conjugate has found application, for example, in the stereoselective Mannich reaction.[79] The Mannich reaction is a widely applied C–C bond-forming reaction used for the construction of β-amino carbonyl structures. By application of optically active auxiliaries, stereoselective conversion has become possible, leading to valuable substrates for employment in medicinal chemistry or natural product synthesis. Tao and co-workers have shown that the addition of 10 mol-% of conjugate **84** to the reaction of cyclohexanone with, for example, *p*-chloraniline and *p*-nitrobenzaldeyhde yields the corresponding Mannich product quantitatively with a diastereomeric ratio of 94:6 and an *ee* of >99% (Scheme 20). This reaction can be carried out in the absence of any additional organic solvent.

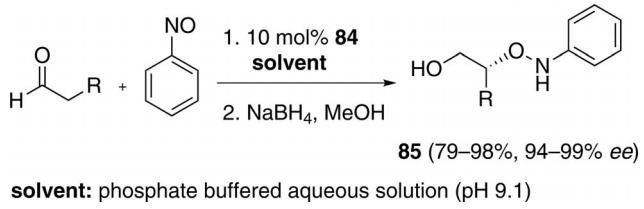


Scheme 20. Mannich reaction using the isosteviol–proline conjugate **84**.

Thus, an asymmetric one-pot three-component Mannich reaction under very mild reaction conditions has been established, offering the opportunity of converting a variety of substrates into the corresponding β-amino carbonyl structures.

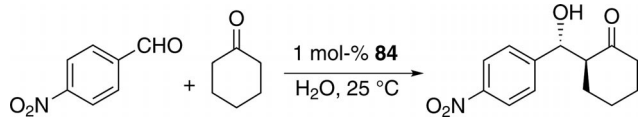
Apart from the Mannich reaction, the (–)-isosteviol-proline conjugate **84** has found application in α-aminoxylation reactions (Scheme 21).[80] Upon employment of 10 mol-% of catalyst **84** in the reactions of aldehydes with nitrosobenzene and subsequent reduction with sodium borohydride, the corresponding products **85** can be obtained in yields of up to 98% with excellent enantioselectivities of up to 99% *ee*. In addition to aldehydes, ketones can also be converted with equally good selectivity.

Furthermore, catalyst **84** can be applied in the asymmetric aldol reaction (Scheme 22).[81] Again, water was used as solvent. In fact, it was found that reactions in solvents other than water proceeded with significantly lower yields, if any



Scheme 21. α-Aminoxylation reaction using **84** as catalyst.

conversion was observed at all. In addition, the catalyst loading could be reduced to 1 mol-%, making this a highly atom-economic process.

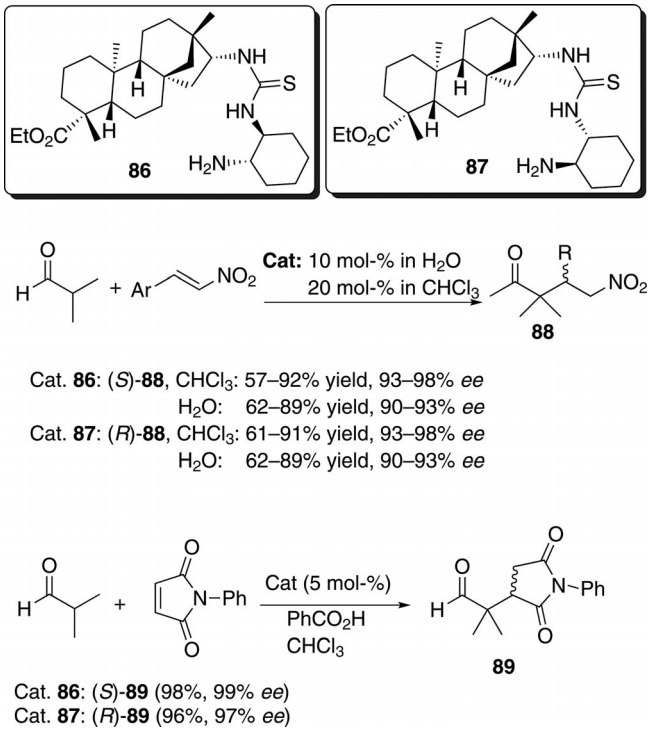


Scheme 22. Aldol reaction with **84** as catalyst.

The proposed transition state of the reaction involves the formation of a hydrophobic chiral pocket on the surface of the water phase due to hydrogen bonding of the hydrophilic proline moieties to water molecules (thus activating the system) and the hydrophobic isosteviol backbone. The reaction takes place within this pocket. Optimal transfer of chirality is ensured as a result of the very confined reaction space.

In addition to the (–)-isosteviol-proline conjugate **84**, thiourea derivatives **86** and **87** are known to induce stereoinformation in asymmetric Michael reactions (Scheme 23).[82] In the reaction of isobutyraldehyde with variously functionalized nitroalkenes, good-to-excellent yields and enantioselectivities for both enantiomeric forms can be observed in both organic and aqueous media.

Furthermore, enantioselective addition of isobutyraldehyde to *N*-phenylmaleimide proceeded to give pyrrolidine derivatives **89** in excellent yields and *ee*s. This presents a highly promising method for the construction of α-chiral succinimide derivatives, a substrate class for which there are only a few procedures available. In combination with other chiral auxiliaries, (–)-isosteviol is a powerful organocatalytic agent in a variety of stereoselective transformations under extremely mild reaction conditions.



Scheme 23. Asymmetric Michael reactions.

4. Conclusions

(–)-Isosteviol is a readily available, inexpensive, ex-chiral-pool building block with unique structural features. The very rigid and concave arrangement of the functional groups is unparalleled. (–)-Isosteviol and a variety of derivatives thereof exhibit significant enhanced biological and cytotoxic activities and are thus promising substrates in medicinal chemistry. A broad range of chemical modifications can be carried out on this particular scaffold. The unique stereochemical arrangement leads to initial and significant applications of (–)-isosteviol as a building block in synthetic organic chemistry, functioning as a chiral auxiliary in various organocatalytic conversions and in the construction of supramolecular systems. Because the use of (–)-isosteviol in organic chemistry is a strongly emerging field, promising applications are expected in due course.

Supporting Information (see footnote on the first page of this article): Preparation and characterization of **2**, **49**, **50**, **51**, **66**.

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