Tetrahedron Letters 53 (2012) 6806–6809

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Fused derivatives of (iso)steviol via pericyclic reactions

Nico Moons [a], Daan Goyens [a], Jeroen Jacobs [b], Luc Van Meervelt [b], Wim M. De Borggraeve [a], Wim Dehaen [a,*]

[a] Division for Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Heverlee, Belgium
[b] Division of Biochemistry, Molecular and Structural Biology, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Heverlee, Belgium

ARTICLE INFO

Article history:
Received 3 August 2012
Revised 24 September 2012
Accepted 2 October 2012
Available online 11 October 2012

Keywords:
Steviol
Isosteviol
Diterpenoids
Pericyclic
Diels–Alder

ABSTRACT

Recently, the diterpenoids steviol and isosteviol, respectively the aglycone and its rearrangement product of the steviol glycosides, have gained a growing interest. Their biological properties have encouraged many scientists to synthesize a considerable amount of analogues. In this Letter, we present three novel (iso)steviol derivatives in which the complex ring structures of the *ent*-kaurene steviol and *ent*-beyerane isosteviol are expanded via two highly stereoselective reaction pathways. For steviol, we expanded the structure by carbonyl ene reaction, followed by either formation of a lactone or a pyrane-3(2*H*)-one in good yields. Isosteviol was converted into a diene, followed by Diels–Alder reaction.

In the latest years, steviol glycosides[1] have gained a growing interest from the general public. The attention given to these compounds was recently increased due to the approval for their use as food additives by the European Commission.[2] Steviol glycosides are natural sweeteners which are extracted from the Paraguayan shrub *Stevia Rebaudiana* in up to 10% of leaf dry weight.[3] Stevioside,[4] the main component of this class of natural products, tastes up to 300 times sweeter than sucrose. The structure of the steviol glycosides consists of a diterpenoid *ent*-kaurene skeleton, linked to one or more glucose groups.[5] Apart from their sweetness, the biological activities of steviol glycosides and their derivatives have been thoroughly investigated. Various beneficial effects have been ascribed to the steviol glycosides and stevioside (Fig. 1) in particular.[4,6] It was shown that stevioside has antihypertensive[7] and antihyperglycemic[8] effects. Furthermore, for the antihyperglycemic activity, the aglycone steviol **1** was more potent than stevioside.[8c] Other effects of the aglycones include antiproliferative[9] and immunomodulary[10] activities. These biological properties, combined with the complex structure of steviol, have inspired many chemists in the past to produce several analogues of the diterpenoid core. They were made either starting from steviol, or from the Wagner-Meerwein rearranged isosteviol **3** (Fig. 1).[11] A large amount of examples can be found in the literature, where several reaction sites of both steviol and isosteviol were used.[12]

In our case, we were particularly interested in analogues containing novel rings constructed on the (iso)steviol moiety. For example, the indole analogue **4** of isosteviol and the formation of isoxazoles (not shown) were recently reported.[13] For steviol, except for the known epoxide **5**,[14] no ring fusions of the *ent*-kaurene skeleton are known. In this Letter, we wish to present the first use of pericyclic reactions to expand the number of rings in the (iso)steviol moiety.

Pericyclic reactions on steviol

Steviol was obtained from stevioside via the conventional oxidative preparation,[15] rather than the time consuming enzymatic

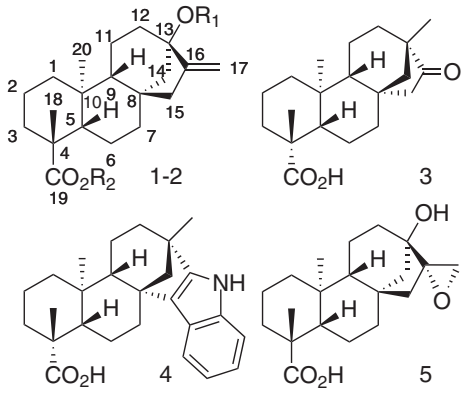


Figure 1. Structures of stevioside **1** (R_1 = –β-Glc-β-Glc(2→1), R_2 = –β-Glc), steviol **2** (R_1 = R_2 = H), isosteviol **3**, and compounds **4–5** with novel rings added to the skeleton.

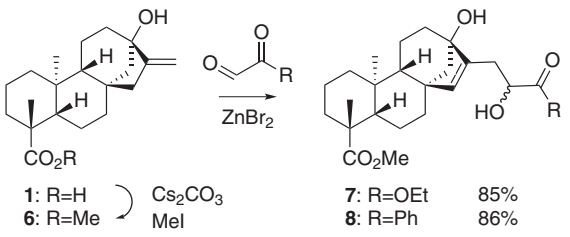
* Corresponding author. Tel.: +32 16 3 27439; fax: +32 16 3 27990.
E-mail address: wim.dehaen@chem.kuleuven.be (W. Dehaen).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.006

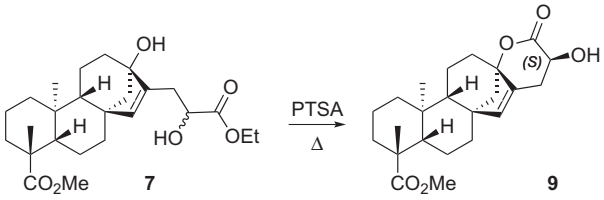
method.[16] To facilitate the purification of all intermediates, we first converted both steviol and isosteviol into their corresponding methyl esters using Cs_2CO_3 and MeI, instead of the known procedure with ethereal diazomethane.[17] Alternatively, the procedure with methyl tosylate can also be used.[18] The carbonyl ene reaction on the methyl ester **6** was first evaluated. There are numerous examples of this reaction in the literature,[19] and recent examples on terpenes as substrates or as target molecules.[20] We first tried the carbonyl ene reaction with ethyl glyoxalate. Without any catalysts, even during heating at higher temperatures (>140 °C) no reaction was observed. Although this reaction is usually successful when using strong Lewis acid catalysts,[19] the rearrangement of steviol ester **6** to its isosteviol analogue was predominant for most conventional acids used in carbonyl ene reactions. To avoid this side reaction, we tried some milder acids and reaction conditions, and $ZnBr_2$ was found to be the best acid catalyst for the carbonyl ene reaction of steviol. The reaction was performed with equimolar amounts of $ZnBr_2$ at room temperature for 2 days. Higher temperatures increased the amount of undesired isosteviol in the reaction mixture. The reaction conditions were optimized for the reaction with ethyl glyoxalate, and the α-hydroxy ester **7** was isolated as a mixture of isomers (85:15) in a total yield of 85%. These reaction conditions were slightly modified for the reaction of steviol ester **6** with phenylglyoxal, resulting in a comparable yield (86%). Surprisingly, for phenylglyoxal only one isomer **8** was formed after 3 days (Scheme 1). As our initial idea was to dehydrate both isomers to their corresponding dienes, no structural elucidation of either α-hydroxy ester **7** or the α-hydroxy ketone **8** was carried out (Scheme 1).

However, upon examining various procedures for the dehydration of products **7** or **8**, we were surprised to find that a cyclization had occurred for both products. Compound **7** was cyclized to the corresponding lactone **9** by refluxing in toluene with 0.1 equiv of *p*-toluenesulfonic acid for 40 minutes. The lactone was isolated in a good yield of 59%, however, the sample contained 2 diastereoisomers in a ratio of 88:12. Their relative amounts were easily calculated via ^{1}H NMR integration. The absolute configuration of both α-hydroxy esters was determined via the ^{1}H coupling constants of the lactone ring. For the main constituent of the mixture, the hydrogen atom in α-position of the ketone group displayed both an axial (12.6 Hz) and an equatorial (6.6 Hz) coupling constant, therefore the hydroxyl group must be in equatorial position. Based on these spectroscopic data, for the major product, the stereogenic center in the lactone ring corresponds with an S-configuration (Scheme 2). Despite several attempts using different separation methods including HPLC, we were unable to separate both diastereomers.

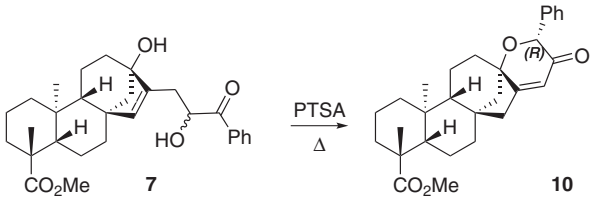
When submitting the phenyl ketone **8** to the same conditions, the reaction outcome was a crystalline product **10**. CIMS measurements revealed a loss of water, while ^{1}H NMR showed the presence of two diastereoisomers in a 93:7 ratio. We were able to isolate the major constituent from the mixture via recrystallization in diethyl ether to afford a yield of 81%, and its structure was determined via 1D and 2D NMR techniques. Compound **10** was found to be a



Scheme 1. Carbonyl ene reactions of steviol methyl ester **6**.



Scheme 2. Formation of a novel lactone **9**. Major constituent shown.



Scheme 3. Cyclization of the α-hydroxy ketone **7** (main diastereomer shown).

2-phenyldihydro-2*H*-pyran-3(4*H*)-one (Scheme 3). The formation of this particular ring can be explained by an addition of the C13 hydroxyl group on the ketone, followed by dehydration of the formed hemiacetal and keto–enol tautomerization. We were able to assign the exact configuration of the stereogenic center in the newly attached ring as the *R*-configuration. In this configuration, the phenyl ring is in the equatorial position, which can also be determined via cross couplings observed in the NOESY spectrum. For validation of our proposed structure, crystallographic X-ray measurements were obtained. The corresponding 3D structure is shown in Fig. 2, and confirms our hypothesis.

Pericyclic reactions on isosteviol

As for steviol **1**, the *ent*-beyerane isosteviol **3** was first converted into its methyl ester **11**[21] by the same procedure. This ester was then submitted to the Grignard reaction with vinyl magnesium bromide. As the ester of isosteviol is rather sterically hindered, the Grignard reaction was performed with multiple equivalents of Grignard reagent. Although this reaction seems quite straightforward, the yield of vinyl adduct **12** was rather low (34%). This was probably due to the instability of the adduct, which seemed to dehydrate and rearrange to multiple unidentifiable side products. Therefore, other pathways to obtain this compound were also investigated. As the addition of ethynyl magnesium bromide to ester **11** was significantly more successful, this ethynyl adduct **13** was reduced with Lindlar's catalyst, resulting in the same product **12**, albeit with a higher total yield of 68%. (Scheme 4). We continued by investigating the dehydration of this vinylated compound **12**. Various methods were tried, but the outcome of these reactions varied significantly. In the presence of a nucleophile, even a weak one, the dehydration often resulted in an addition at the formed carbocation, rather than the formation of the desired diene. For example, we were able to characterize the addition of toluene to the vinyl adduct **12** by refluxing in the presence of PTSA. As an alternative route, the dehydration of acetylene derivative **13** was investigated. The outcome for these reactions when using acid (e.g. 98% sulfuric acid or 85% phosphoric acid) was roughly the same. Surprisingly, when using thionyl chloride as a dehydrating agent, a chloroallene[22] **14** was formed instead of the desired dehydrated compound (Scheme 4). We were able to optimize this reaction to a yield of 52%, yet no further reactions on the allene **14** were carried out.

As the instability of the intermediate carbocation after removal of the hydroxyl group was obvious, we envisaged a one pot dehy-

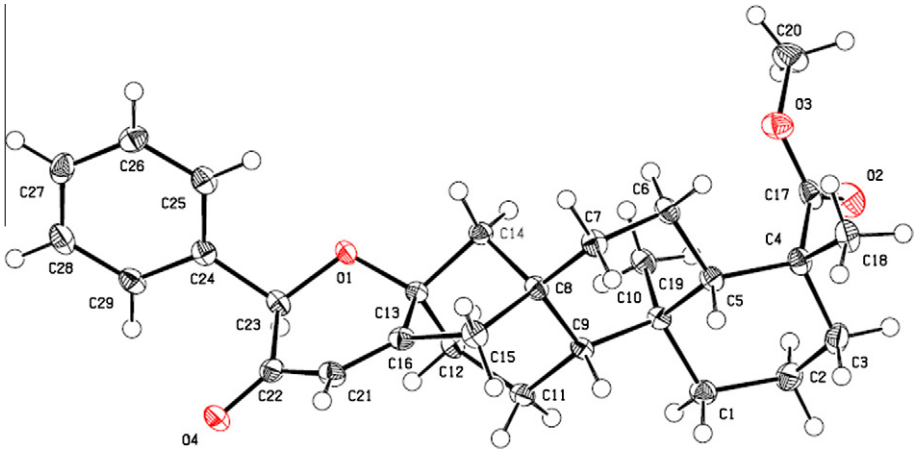
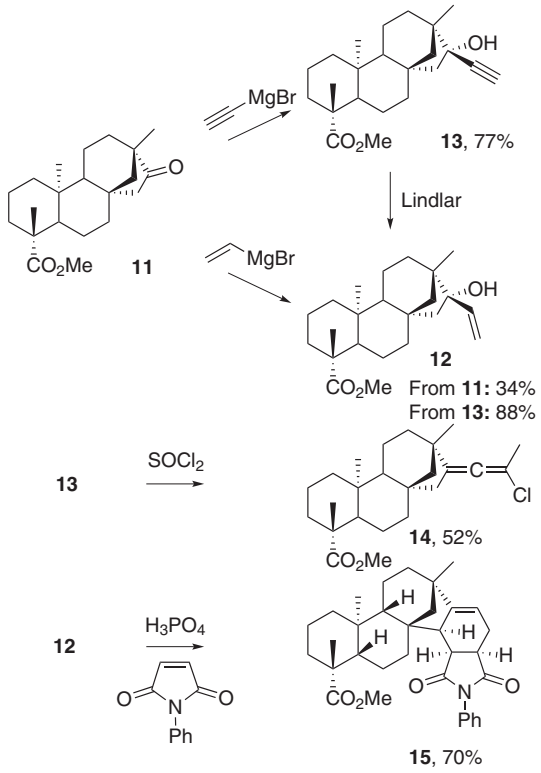


Figure 2. Crystal structure of the 2*H*-pyran-3(4*H*)-one **10**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 4. Synthesis of the first Diels–Alder addition on the isosteviol moiety.

dration followed by in situ trapping of the diene via a Diels–Alder reaction. For this reaction, compound **12** was dissolved in phosphoric acid (85%), and an excess amount of *N*-phenylmaleimide was added. After heating at 110 °C for 24 h all starting materials had been converted, and the desired cyclized product **15** was isolated in a yield of 70% (Scheme 4). Remarkably, only one isomer was formed. We were able to determine the configuration of this Diels–Alder adduct, which resulted of an *endo*-addition of the dienophile, by 2D NMR experiments. In the ^{1}H NMR spectrum, a clear downfield shift was observed for the equatorial hydrogen on C7, which suggested the proximity of the carbonyl group C26. Furthermore, when looking at H15, a very small coupling constant (below 1 Hz) was observed, which can only exist when H15 and H25 are positioned in a twisted cis-conformation. NOESY experiments confirmed this hypothesis, and the configuration of C15 could also be

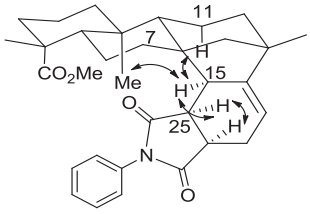


Figure 3. NOESY couplings observed in Diels–Alder adduct **15**, which lead to the assignment of the configuration.

confirmed by the proximity of H15 with the methyl group of C20 and the axial hydrogen atom on C11, as seen in the NOESY experiment. All measured NOESY cross peaks are shown in Figure 3.

Acknowledgments

The authors thank the F.W.O., the K.U. Leuven and the Ministerie voor Wetenschapsbeleid for financial support. N.M. thanks the IWT for a PhD fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.006.

References and notes

1. Kinghorn, A. D. *Stevia: the genus Stevia*; Taylor & Francis: London, New York, 2002. p 211.
2. Official Journal of the European Union 12/11/2012, L295/205.
3. Bridel, M.; Lavieille, R. *Bull. Soc. Chim. Biol.* **1931**, *13*, 781–796.
4. Geuns, J. M. *Phytochemistry* **2003**, *64*, 913–921.
5. (a) Mosettig, E.; Nes, W. R. *J. Org. Chem.* **1955**, *20*, 884–899; (b) Wood, H. B.; Allerton, R.; Diehl, H. W.; Fletcher, H. G. *J. Org. Chem.* **1955**, *20*, 875–883.
6. Brahmachari, G.; Mandal, L. C.; Roy, R.; Mondal, S.; Brahmachari, A. K. *Arch. Pharm.* **2011**, *344*, 5–19.
7. Chan, P.; Tomlinson, B.; Chen, Y. J.; Liu, J. C.; Hsieh, M. H.; Cheng, J. T. *Br. J. Clin. Pharmacol.* **2000**, *50*, 215–220.
8. (a) Chen, J. G.; Jeppesen, P. B.; Nordentoft, I.; Hermansen, K. *Am. J. Physiol. Endocrinol. Metab.* **2007**, *292*, E1906–E1916; (b) Gregersen, S.; Jeppesen, P. B.; Holst, J. J.; Hermansen, K. *Metabolism* **2004**, *53*, 73–76; (c) Jeppesen, P. B.; Gregersen, S.; Poulsen, C. R.; Hermansen, K. *Metabolism* **2000**, *49*, 208–214.
9. Wong, K. L.; Lin, J. W.; Liu, J. C.; Yang, H. Y.; Kao, P. F.; Chen, C. H.; Loh, S. H.; Chiu, W. T.; Cheng, T. H.; Lin, J. G.; Hong, H. J. *Pharmacology* **2006**, *76*, 163–169.
10. Boonkaewwan, C.; Ao, M.; Toskulkao, C.; Rao, M. C. *J. Agric. Food Chem.* **2008**, *56*, 3777–3784.
11. Mosettig, E.; Beglinger, U.; Dolder, F.; Lichti, H.; Quitt, P.; Waters, J. A. *J. Am. Chem. Soc.* **1963**, *85*, 2305–2309.

12. Moons, N.; De Borggraeve, W.; Dehaen, W. *Curr. Org. Chem.* **2011**, *15*, 2731–2741.
13. Wu, Y.; Liu, C. J.; Liu, X.; Dai, G. F.; Do, J. Y.; Tao, J. C. *Helv. Chim. Acta* **2010**, *93*, 2052–2069.
14. Mori, K.; Matsui, M. *Tetrahedron Lett.* **1970**, *11*, 3287–3288; Terai, T.; Ren, H.; Mori, G.; Yamaguchi, Y.; Hayashi, T. *Chem. Pharm. Bull. (Tokyo)* **2002**, *50*, 1007–1010.
15. Ogawa, T.; Nozaki, M.; Matsui, M. *Tetrahedron* **1980**, *36*, 2641–2648.
16. Wehrli, C. Process for the enzymatic preparation of steviol from stevioside. **2011**, WO 2011/089031 A1.
17. Coates, R. M.; Bertram, E. F. J. *J. Org. Chem.* **1971**, *36*, 2625.
18. Bomkamp, M.; Artiukhov, A.; Kataeva, O.; Waldvogel, S. R. *Synthesis* **2007**, 1107–1114.
19. Berrisford, D. J.; Bolm, C. *Angew. Chem. Int. Ed.* **1995**, *34*, 1717–1719; Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, *64*, 9003–9031; Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.
20. Abad, A.; Agullo, C.; Cunat, A. C.; Navarro, I.; de Arellano, C. R. *J. Chem. Res. Synop.* **2001**, 90–91; Ashirov, R. V.; Appolonova, S. A.; Plemenkov, V. V. *Chem. Nat. Compd.* **2006**, *42*, 434–438; Page, P. C. B.; Gambera, G.; Hayman, C. M.; Edgar, M. *Synlett* **2006**, 3411–3414.
21. Coates, R. M.; Kang, H. Y. *J. Org. Chem.* **1987**, *52*, 2065–2074.
22. Stammann, G.; Rehman, Z.; Griesbaum, K. *Chem. Ber.-Recl.* **1980**, *113*, 3103–3111; Vincze, I.; Lokos, M.; Bakos, T.; Dancsi, A.; Mak, M. *Steroids* **1993**, *58*, 220–224.