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Synthetic Studies towards Guaianolide Sesquiterpene Lactones

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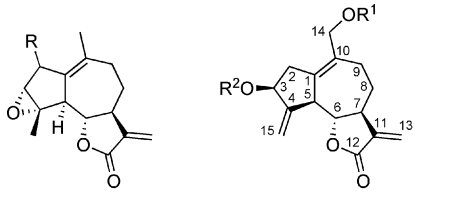
A promising synthetic route towards bioactive guaianolide sesquiterpene lactones is presented. The strategy is based on a recently invented multicomponent reaction (MARDi cascade) and subsequent highly chemoselective and domino transformations for the expeditious stereoselective preparation of the tricyclic core of the natural products.

Introduction

The bicyclo[5.3.0]decane ring system is present in numerous classes of naturally occurring sesquiterpenes[1] and diterpenes.[2] Guaianolides, of which compounds **1** and **2** are the archetype (Figure 1),[3] are by far the most common sesquiterpene lactones (STLs) in natural products with this bicyclic framework. They usually exhibit a *trans*-γ-lactone ring fused to the C^6–C^7 bond of the bicycle or, less often, to the C^7–C^8 bond, and have been the subject of considerable synthetic[4] and biological studies.[1,5] In our continuous effort towards eco-compatible synthetic routes to valuable molecules involving domino and/or multicomponent reactions (MCRs), we have recently developed the MARDi cascade, a Michael-initiated MCR which allows a diastereoselective access to a variety of carbo- and heterocyclic seven-membered rings under user- and environmentally friendly conditions.[6] The application of multicomponent/domino reactions[7] to target-oriented synthesis has been conceptualized as early as 1917 by Robinson, and its advantages have been demonstrated with the efficient one-pot synthesis of the bridged bicyclic alkaloid tropinone by using a double Mannich three-component reaction.[8] Since then the strategy has remained under-exploited for many decades.[9] Herein we wish to report our early results on a promising synthetic approach to guaianolide STLs involving the MARDi cascade.



1a: R = β-OAc, α-H
1b: R = =O

2: R^1, R^2 = H, various esters

Figure 1. Representative guaianolides.

Results and Discussion

The MARDi cascade with the β-oxo ester **3** and crotonaldehyde yields the cycloheptanol **4** in 94% yield as the only detectable isomer (Scheme 1).[6] Of crucial importance for the synthetic applications of the MARDi cascade to target-oriented synthesis is the chemo-differentiation of the two carboxylate groups in the product. In the solid-state packing structure of **4**,[10] an intermolecular hydrogen bond is evidenced between the hydroxy group and the carbonyl group of the β-hydroxy ester of a neighboring molecule (d = 1.975 Å, see Supporting Information). In the gas phase, the calculated optimum geometry of **4** showed the possible occurrence of an intramolecular hydrogen bond between the hydroxy group and the carbonyl group of the adjacent methyl ester (d = 2.195 Å, see Supporting Information). We anticipate that such a hydrogen bond would exist in solution and attempted the chemoselective reduction of the β-hydroxy ester to a 1,3-diol. To our delight, the treatment of **4** with excess sodium borohydride yielded efficiently the expected diol **5** where the three carbon atoms bonded to oxygen atoms can now be easily selectively manipulated.[11]

With the application of the MARDi cascade to guaianolide STLs in mind, the β-oxo ester **3** and the model aldehyde **6** were allowed to react under the optimized conditions of the cascade to give the expected bicyclo[5.3.0]decanol **7** as a mixture of at least 5 diastereomers, together with some saponified and dehydrated products as previously observed in related cases (Scheme 2).[6] The saponified fraction of the material was esterified back to the diesters with (trimethylsilyl)diazomethane,[12] the two fractions were combined and purified by flash chromatography to afford the bicy-

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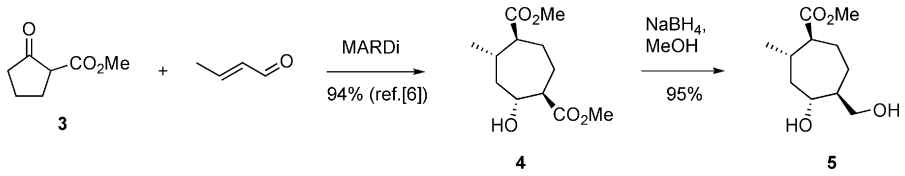
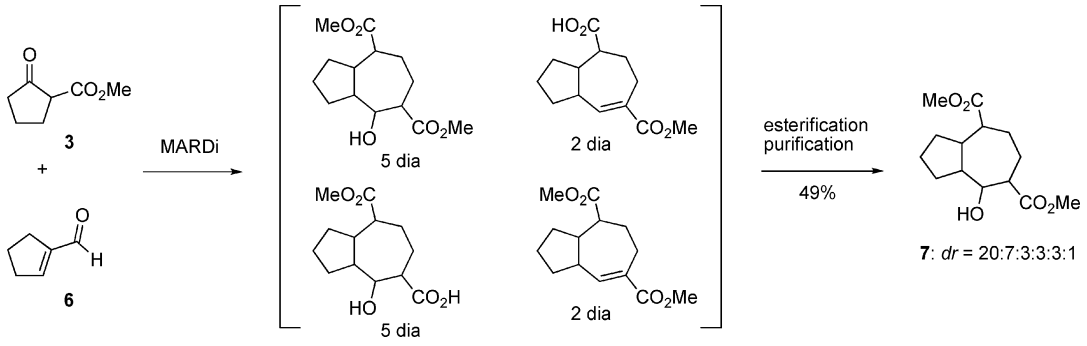


Scheme 1.



Scheme 2.

clo[5.3.0]decanol **7** as a mixture of 6 detectable diastereomers (*dr* = 20:7:3:3:3:1) in 49% yield (Scheme 2). The relative stereochemistry of the two major diastereomers of **7** was deduced from X-ray diffraction analysis of a monocrystal obtained by slow concentration of a sample (in chloroform) containing only the two major diastereomers of **7** in a 2:1 ratio. To our surprise, the X-ray analysis revealed that both diastereomers nicely co-crystallized, and left the major diastereomer almost pure as an oil at room temperature.[10] From this analysis and some additional NMR studies on the pure major isomer, the two major diastereomers were assigned the structures depicted in Figure 2. We may note that these two diastereomers only differ at the C^{10} atom (numerotation of guaianolides) and have the same conformation of the south part of the bicyclic system, at least in the solid state.

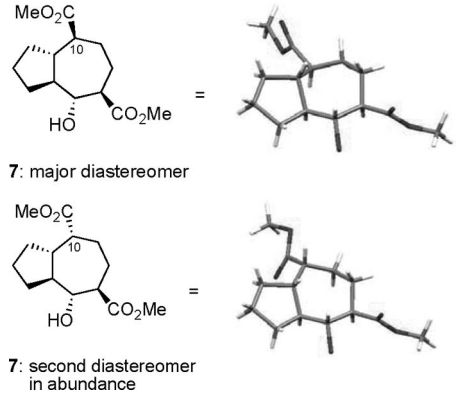
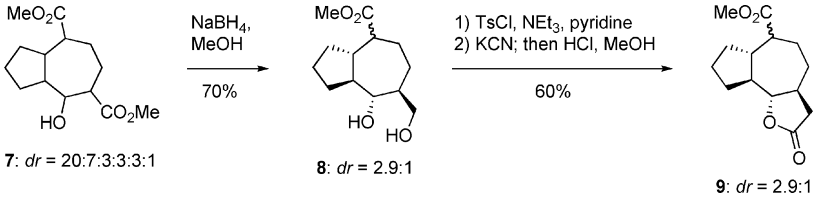


Figure 2. X-ray diffraction analysis of **7**.

The treatment of **7** (*dr* = 20:7:3:3:3:1) with excess sodium borohydride resulted in the almost quantitative chemoselective reduction of the β-hydroxy ester group *of only the two major isomers* yielding a 2.9:1 mixture of diols **8** (Scheme 3), the remaining material being composed only by the unreactive four minor diastereomers of **7**. As in the case of **4**, a rational for the chemoselective reduction was provided by semiempirical calculations, which confirmed the possible occurrence of an activating intramolecular hydrogen bond in the two major diastereomers of **7** (see Supporting Information). The sharp difference of reactivity observed between the six diastereomers of **7** suggests that only the two most abundant ones can adopt a conformation stabilized by an intramolecular hydrogen bond under the reaction conditions. Thus, the stereoselectivity of the MARDi cascade associated with the high chemoselectivity of this reduction provides a *two-step only* stereocontrolled synthetic access to the diols **8** (*dr* = 2.9:1) with four contiguous asymmetric carbon atoms and a remaining enolizable position at the non-controlled center. Following our plan to demonstrate the relevance of the MARDi cascade for the total synthesis of guaianolide STLs, we studied the installation of a γ-lactone from the diols **8** by homologation at the primary



Scheme 3.

alcohol position. This was realized in a straightforward manner by replacement of the corresponding tosylate with a cyano group, followed by in situ hydrolysis and spontaneous cyclization (domino reaction) to afford the tricyclic compound **9** (Scheme 3). Overall, compound **9**, which is closely related to guaianolides **1** and **2**, has been obtained in four[13] chemical operations from the renewable β-oxo ester **3** and the aldehyde **6**,[14] involving an MCR and a domino process.

Conclusions

The combination of the MARDi cascade, a recently invented MCR, with highly chemoselective and domino transformations allowed the expeditious synthesis of compound **9**, which exhibits the functionalized tricyclic framework of guaianolides, and four contiguous controlled stereocenters. In the current era where the efficiency of a synthetic sequence is more than ever related to its conciseness, the synthetic route presented herein is expected to translate into several efficient total syntheses of naturally occurring guaianolides and their derivatives.

Experimental Section

Compound 7: To a solution of **3** (5.05 g, 35.5 mmol) in methanol (460 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5.3 mL, 35.5 mmol), and the reaction mixture was stirred under argon at 0 °C for 10 min. The aldehyde **6** (4.42 g, 46.0 mmol) was then introduced, and the reaction mixture was slowly warmed to 24 °C and stirred for 64 h. The resulting yellow-brown solution was partially concentrated under reduced pressure to remove most of the methanol, hydrolyzed with water, and the resulting aqueous phase extracted three times with ethyl acetate. The combined organic layers were washed twice with brine, dried with anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product #1 (4.1 g). The previous aqueous layer was acidified with 2 N HCl (pH = 1) and extracted again three times with ethyl acetate, the organic layers were combined, dried with anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product #2 (6.0 g). This material was immediately placed in dichloromethane/methanol (4:1) (380 mL) at 0 °C and treated with a 2.0 M (trimethylsilyl)diazomethane solution in diethyl ether (11.6 mL, 23.2 mmol) for 10 min, whereupon glacial acetic acid (0.2 mL) was added. The solution was concentrated under vacuum, diethyl ether (100 mL) was added, and the organic solution washed with saturated sodium hydrogen carbonate and brine, dried with anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the crude product #3. The crude products #1 and #3 were combined and purified by flash chromatography on silica gel eluting with increasing amounts of ethyl acetate in petroleum ether ether to give 4.70 g (49%) of **7** (*dr* = 20:7:3:3:3:1) as a colorless oil. R_f = 0.47–0.77 [AcOEt/petroleum ether ether (50:50)]; the homogeneity of the mixture was proven by elemental analysis. One of the fractions obtained after chromatography containing essentially the two major diastereomers (*dr* = 2:1) provided some colorless crystals (slow evaporation of chloroform, prism, m.p. 49 °C) suitable for X-ray analysis (see text and ref.[10]). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$); selected resonances: δ = 3.71 (s, 3 H), 3.66 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2 (C), 175.3 (C), 76.8 (CH), 54.6 (CH), 51.2 (CH_3), 51.0 (CH_3), 48.7 (CH), 47.9 (CH), 41.1 (CH), 32.8 (CH_2), 31.3 (CH_2), 28.0 (CH_2), 23.3 (CH_2), 23.2 (CH_2) ppm. Second isomer in abundance: ^{1}H NMR (300 MHz, $CDCl_3$); selected resonances: δ = 3.65 (s, 3 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7 (C), 175.5 (C), 77.6 (CH), 59.8 (CH), 55.5 (CH_3), 50.7 (CH_3), 44.5 (CH), 44.1 (CH), 39.9 (CH), 31.1 (CH_2), 30.8 (CH_2), 24.4 (CH_2), 23.4 (CH_2), 20.4 (CH_2) ppm. Third isomer in abundance: ^{1}H NMR (300 MHz, $CDCl_3$); selected resonances: δ = 3.63 (s, 3 H), 3.61 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6 (C), 175.0 (C), 73.4 (CH), 52.6 (CH), 51.5 (CH_3), 51.3 (CH_3), 50.4 (CH), 45.3 (CH), 41.5 (CH), 31.5 (CH_2), 29.6 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 24.1 (CH_2) ppm. Fourth isomer in abundance: ^{1}H NMR (300 MHz, $CDCl_3$); selected resonances: δ = 3.64 (s, 3 H), 3.57 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1 (C), 176.2 (C), 73.2 (CH), 51.8 (CH_3), 51.4 (CH_3), 45.9 (CH), 45.4 (CH), 45.2 (CH), 40.8 (CH), 31.2 (CH_2), 28.7 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 24.6 (CH_2) ppm. The NMR spectroscopic data of the other isomers could not be extracted with high confidence from the set of complex spectra we have analyzed. Mixture of isomers: MS (ESI+): *m*/*z* = 271 $[M + H]^+$, 293 $[M + Na]^+$, 309 $[M + K]^+$. Fraction containing 5 of the 6 isomers: $C_{14}H_{22}O_5$ (270.32): calcd. C 62.20, H 8.20; found C 61.75, H 8.42.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for **5**, **8** and **9**, crystallographical and computational study of the hydrogen bonds in **4**, computational study of the hydrogen bond in **7**, copies of ^{1}H and ^{13}C NMR spectra for **5** and the two diastereomers of **9**.

Acknowledgments

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[1] B. M. Fraga, *Nat. Prod. Rep.* **2007**, *24*, 1350–1381, and previous reports in this series.
[2] J. R. Hanson, *Nat. Prod. Rep.* **2007**, *24*, 1332–1341, and previous reports in this series.
[3] Isolation of **1a**: a) F. Bohlmann, C. Zdero, R. M. King, H. Robinson, *Phytochemistry* **1984**, *23*, 1187–1188; of **1b**: b) A. Ortega, R. A. Toscano, E. Maldonado, *Phytochemistry* **1998**, *49*, 1085–1090; of **2**: c) F. Bohlmann, C. Zdero, R. M. King, H. Robinson, *Phytochemistry* **1989**, *28*, 517–526.
[4] For a review, see: A. Schall, O. Reiser, *Eur. J. Org. Chem.* **2008**, 2353–2364.
[5] For recent examples involving compounds **1** or **2**, see: a) B. Siedle, A. J. García-Piñeres, R. Murillo, J. Schulte-Mönting, V. Castro, P. Rüngeler, C. A. Klaas, F. B. Da Costa, W. Kisiel, I. Merfort, *J. Med. Chem.* **2004**, *47*, 6042–6054; b) M. T. Lindenmeyer, A. Hrenn, C. Kern, V. Castro, R. Murillo, S. Müller, S. Laufer, J. Schulte-Mönting, B. Siedle, I. Merfort, *Bioorg. Med. Chem.* **2006**, *14*, 2487–2497; c) S. Wagner, A. Hofmann, B. Siedle, L. Terfloth, I. Merfort, J. Gasteiger, *J. Med. Chem.* **2006**, *49*, 2241–2252.
[6] Y. Coquerel, M.-H. Filippini, D. Bensa, J. Rodriguez, *Chem. Eur. J.* **2008**, *14*, 3078–3092.
[7] For recent monographs, see: a) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; b) *Domino Reactions in Organic Synthesis* (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, Weinheim, **2006**.
[8] R. Robinson, *J. Chem. Soc.* **1917**, 762–768.
[9] For recent selected examples, see: a) J. Isaacson, M. Loo, Y. Kobayashi, *Org. Lett.* **2008**, *10*, 1461–1463; b) J. Pospíšil, I. E.

Markó, *J. Am. Chem. Soc.* **2007**, *129*, 3516–3517; c) A. Dömling, B. Beck, U. Eichelberger, S. Sakamuri, S. Menon, Q.-Z. Chen, Y. Lu, L. A. Wessjohann, *Angew. Chem. Int. Ed.* **2006**, *45*, 7235–7239; d) A. B. Smith III, D.-S. Kim, *J. Org. Chem.* **2006**, *71*, 2547–2557.

[10] CCDC-620411 (for **4**) and -697454 [for **7** (co-crystal of the two major diastereomers)] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] This unusual reactivity of $NaBH_4$ with β-hydroxy esters has previously been observed, though not fully rationalized, see: a) N. Finch, L. D. Vecchia, J. J. Fitt, R. Stephani, I. Vlattas, *J. Org. Chem.* **1973**, *38*, 4412–4424; b) K. C. Nicolaou, T. K. Chakraborty, Y. Ogawa, R. A. Daines, N. S. Simpkins, G. T. Furst, *J. Am. Chem. Soc.* **1988**, *110*, 4660–4672.

[12] a) N. Hashimoto, T. Aoyama, T. Shiori, *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478. For the mechanism, see: b) E. Kühnel, D. D. P. Laffan, G. C. Lloyd-Jones, T. Martínez del Campo, I. R. Shepperson, J. L. Slaughter, *Angew. Chem. Int. Ed.* **2007**, *46*, 7075–7078.

[13] Five chemical operations if the re-esterification of a part of the crude material of the MARDi cascade is included.

[14] The commercially available β-oxo ester **3** is derived from dimethyl adipate (Dieckmann cyclization), whereas the aldehyde **6** is obtained either from cyclohexene or adipaldehyde according to a one-pot protocol: E. D. Bergmann, A. Becker, *J. Am. Chem. Soc.* **1959**, *81*, 221–225, and references cited therein.

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