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Towards the total synthesis of tonantzitlolone—preparation of key fragments and the complete carbon backbone

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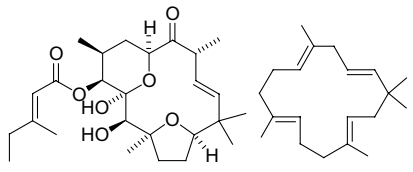
Abstract—The first synthetic advances towards the novel diterpenoid tonantzitlolone **1** are described. The key steps in the synthesis involve a chromium(II) Reformatsky reaction, a diastereoselective C_1 extension and an expeditious aldol coupling step of two advanced precursors.

In 1997, Jakupovic and Jeske isolated a new diterpenoid from the endemic Mexican plant *Stillingia sanguinolenta* with so far unknown absolute stereochemistry and named it tonantzitlolone **1**.[1] Besides flexibilene **2**[2] it is the only 15-membered macrocyclic diterpene found in nature so far. Two internal five- and six-membered rings of which the latter is a δ-lactol ring and an unsaturated side chain complement important structural features of this diterpene. Strong internal hydrogen bonds between the hydroxy group at C-10 and the ester oxygens of the side chain and in particular between the lactol hydroxy group and the furan oxygen atom were noted,[1] which give the molecule a very rigid almost globular overall structure. This compactness is further enhanced by a set of five methyl substituents, which branch off the macrocycle.



1 **2**

Preliminary biological evaluation[3] indicated high activity and selectivity against human breast and kidney cancer cell lines. The novel highly complex and unique structure together with its promising biological activity and its limited supply makes **1** an ideal candidate for total synthesis.

Retrosynthetic analysis leads to aldehyde **3** and ketone **4** both of which are similar in size and complexity. Further disconnection yielded twice (*R*)-β-hydroxy isobutyrate **5**, the acylated oxazolidinone **6**, and geraniol **7** as starting materials (Scheme 1).

Starting from the commercially available isobutyrate **5** building blocks **8** and **9** were prepared straightforwardly as reported in the literature. The free hydroxyl group in **5** was protected as TBDPS-ether, followed by reduction of the ester.[4] Oxidation was then achieved with the reagent system diacetoxybromate(I) resin **10**/TEMPO[5] yielding enantiomerically pure aldehyde **8** in almost quantitative yield.

Compound **9** was prepared by TES silylation, reduction, and subsequent iodination using a polymer-assisted variant[6,7] of the Appel protocol (Scheme 2).[8]

With these building blocks in hand, we approached the connection of both fragments via a C_1-synthon. This procedure is based on a protocol developed in our laboratories.[9] Thus, phosphine oxide **12** was lithiated at

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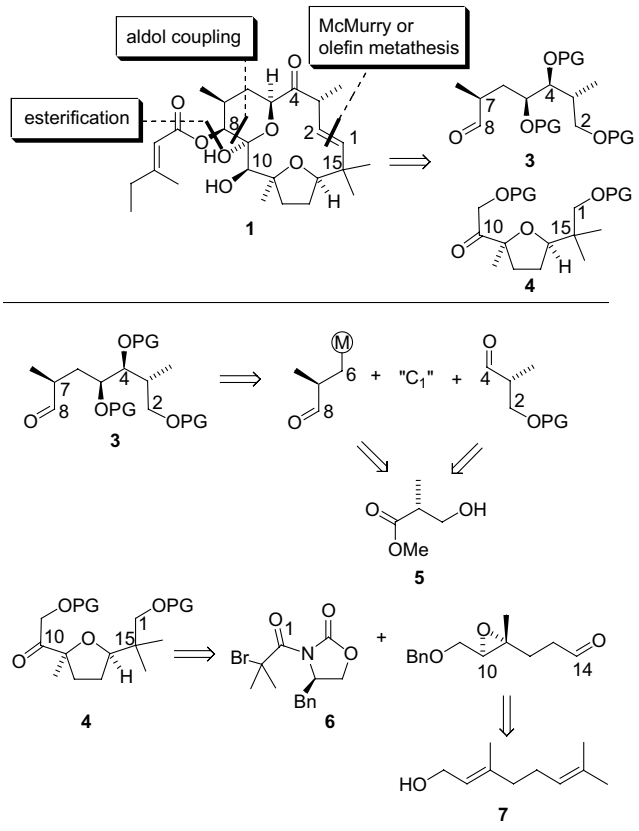
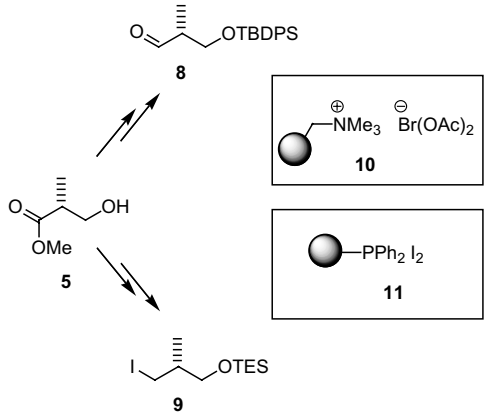


Scheme 1.



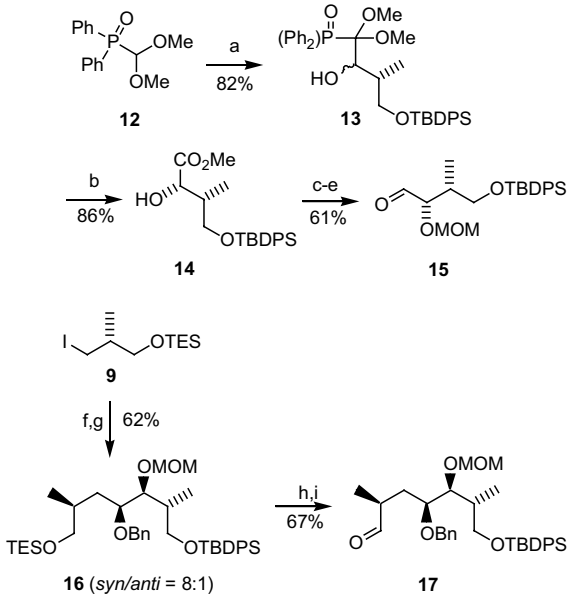
Scheme 2.

low temperature and was reacted with aldehyde **8**, which yielded addition products **13** (*syn*/*anti* = 3:1) upon hydrolysis. This mixture of alcohols was subjected to eliminating conditions using KO*t*Bu and furnished the corresponding labile *O*,*O*-ketene acetal. This intermediate delivered the α-hydroxy ester **14** after treatment under asymmetric dihydroxylation conditions with AD-mix α.[10]

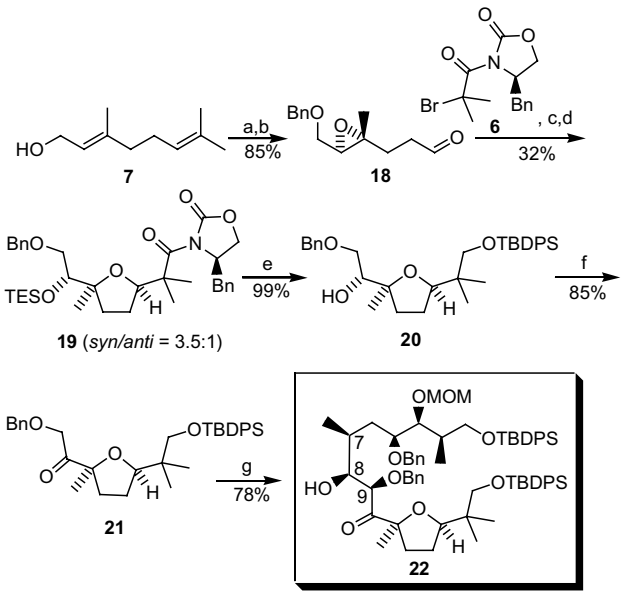
Further protection of the alcohol function as methoxymethyl ether and a standard reduction–oxidation sequence produced aldehyde **15**, which is ideally suited for a chelation-controlled addition of the organomagnesium species prepared from **9**. During this reaction complete dissolution of the magnesium salt has to be secured for obtaining best stereocontrol. The diastereomeric ratio (*syn*/*anti* = 8:1) could be determined at the stage of the benzyl ether derivatives **16**. Removal of the primary triethylsilyl ether and polymer-assisted oxidation of the liberated alcohol using reagent **10** as cooxidant for TEMPO yielded aldehyde **17**, which had to serve as a coupling partner in an aldol reaction with the 'southern hemisphere' **4** (Schemes 3 and 4).

Starting from geraniol **7**, epoxyaldehyde **18** is prepared via the asymmetric Sharpless epoxidation,[11] benzylation and subsequent ozonolysis.[12] This labile aldehyde was reacted with the α-bromoacyl oxazolidinone **6** in the presence of $CrCl_2$ as described by Wessjohann and co-workers.[13] This reaction directly yielded tetrahydrofuran **19** as a mixture of diastereomers (*syn*/*anti* = 3.5:1) in one step and in moderate yield.[14] Separation was eased after *O*-silylation using TESCl as silylating agent. After reductive removal of the chiral auxiliary and desilylation the intermediate diol was transformed into the TBDPS-silylether **20**. Oxidation of the remaining secondary alcohol functionality with Dess–Martin's periodinane[15] furnished α-alkoxy ketone **21**, the targeted coupling partner for aldehyde **17**.

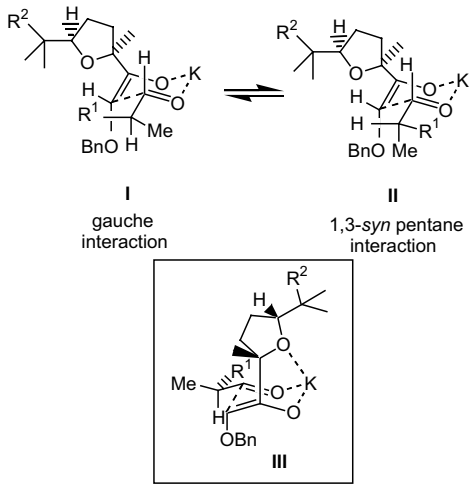
After considerable experimentation[16] KHMDS proved to be the best choice for the deprotonation of **21** and the following aldol reaction with aldehyde **17**. The adduct **22** could be isolated as single diastereomer in 78% yield.[17,18]



Scheme 3. Reagents and conditions: (a) LDA (3.5 equiv), THF, −110 °C, 10 min, then addition of **8**; (b) KO*t*Bu (1.1 equiv), THF, 0 °C, 15 min, then AD-mix α, $MeSO_2NH_2$, H_2O–*t*BuOH (1:1); (c) MOMCl, *i*PrNEt$_2$, 4-DMAP, CH_2Cl_2, 40 °C (83%); (d) dibal-H, (3 equiv in toluene), CH_2Cl_2, −78 °C to rt (83%); (e) **10**, cat. TEMPO, CH_2Cl_2, 50 °C, 2 h (88%); (f) *t*BuLi (2 equiv), $MgBr_2$–Et_2O, pentane–Et_2O (1.5:1), −78 °C, then **15**, 30 min (82%); (g) BnBr (12 equiv), Bu_4NI (14 equiv), NaH, 70 °C, 8 h (82%); (h) CSA, CH_2Cl_2, rt (85%); (i) **10**, cat. TEMPO, CH_2Cl_2, 50 °C, 2 h (96%).



Scheme 4. Reagents and conditions: (a) $Ti(OiPr)_4$, *t*BuOOH, (−)-DET, ms, CH_2Cl_2, then KO*t*Bu, BnBr, Et_4NI, THF, rt (95% for two steps); (b) O_3, CH_2Cl_2, −78 °C, PPh_3, −78 °C to 25 °C (89%); (c) **6**, $CrCl_2$, THF, rt, (40%); (d) TESCl, imidazole, 4-DMAP, CH_2Cl_2, (79%); (e) $LiBH_4$, THF, MeOH, 0 °C, (99%), then TBAF, THF, rt followed by TBDPSCl, imidazole, 4-DMAP, DMF, 0 °C to rt (99%); (f) Dess–Martin periodinane, CH_2Cl_2, rt (85%); (g) KHMDS, THF, −78 °C, then **17** (78%).



Very few examples of aldol reactions comprising a *Z*-enolate derived from an α-alkoxy ketone and an α-chiral aldehyde can be found in the literature.[19] By combining the Felkin–Anh rule with the Zimmerman–Traxler model (cf. **I** and cf. **II**) formation of the 7,8-*syn*,*syn* diastereomer can be expected. However, ketone **22** clearly has a 7,8-*anti*-8,9-*syn* stereochemical relationship, which could have originated from the *anti*-Felkin transition state (cf. **III**). It can be assumed that transition state **II** suffers from severe 1,3-*syn*-pentane interaction.[20] In addition, rotamer **I** has an unfavorable *gauche* relationship. Both of these interactions are reduced to a minimum in transition state **III** for which some evidence has been collected before.[21]

In conclusion, we prepared key fragments **17** and **21** for the convergent synthesis of tonantzitlolone **1** in a straightforward manner starting from readily available building blocks from the chiral pool. Our synthetic approach includes reactions rarely used in natural product synthesis such as the chromium Reformatsky reaction, a protocol for the asymmetric acylation of aldehydes and the use of polymer-supported reagents.

Work is in progress to complete the total synthesis of **1** and derivatives to establish structure–activity relationships.

Acknowledgements

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References and notes

1. Jeske, F. Ph.D. thesis, TU Berlin Germany, 1997.
2. (a) Hérin, M.; Colin, M.; Tursch, B. *Bull. Soc. Chim. Belg.* **1976**, *85*, 707–719; (b) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Schönholzer, P.; Coll, J. C. *Aust. J. Chem.* **1978**, *31*, 1817–1824.
3. Jakupovic, J.; Jas, J., unpublished results.
4. (a) Mulzer, J.; Mantoulidis, A.; Oehler, E. *J. Org. Chem.* **2000**, *65*, 7456–7467; (b) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096–6107.
5. (a) Sourkouni-Argirusi, G.; Kirschning, A. *Org. Lett.* **2000**, *2*, 4759–4760; (b) Brünjes, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Adv. Synth. Catal.* **2003**, 635–642.
6. (a) Caputo, R.; Cassano, E.; Longobardo, L.; Palombo, G. *Tetrahedron Lett.* **1995**, *36*, 167–168; (b) Caputo, R.; Ferreri, C.; Palombo, G. *Tetrahedron* **1995**, *51*, 12337–12350.
7. Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679.
8. (a) Smith, N. D.; Kocienski, P. J.; Street, S. D. A. *Synthesis* **1996**, 652–666; (b) Ramachandran, P. V.; Prabhudas, B.; Pratihar, D.; Chandra, J. S.; Reddy, M. V. R. *Tetrahedron Lett.* **2003**, *44*, 3745–3748.
9. (a) Kirschning, A.; Dräger, G.; Jung, A. *Angew. Chem.* **1997**, *109*, 253–255; (b) Monenschein, H.; Dräger, G.; Jung, A.; Kirschning, A. *Chem. Eur. J.* **1999**, *5*, 2270–2280.
10. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
11. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780; (b) Marty, M.; Stoeckli-Evans, H.; Neier, R. *Tetrahedron* **1996**, *52*, 4645–4658.
12. Van Hijfte, L.; Kolb, M. *Tetrahedron* **1992**, *48*, 6393–6402.
13. Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36, and references cited therein.

14. When the *S*-configured enantiomer of **6** was employed the corresponding Reformatsky products **19** were formed as a diastereomeric mixture (*syn*/*anti* = 1:2).
15. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
16. LDA, Bu_2BOTf/Et_3N, Cy_2BCl/Et_3N, $TiCl_4/(iPr_2)EtN$, Me_2AlCl/Et_3N were not successful in the enolization step.
17. Spectroscopic data of compounds **19**, **21**, and **22**: **19**: colorless oil, IR (ATR): 2954, 2875, 1780, 1687, 1455, 1388, 1348, 1263, 1190, 1102, 1015, 967, 735, 700. MS (ESI) *m*/*z*: 618 ($M+Na^+$), HRMS (ESI) calcd for $C_{34}H_{49}NO_6Na^+$ ($M+Na^+$): 618.3227, found: 618.3229. $[\alpha]_D^{20}$ −17.1 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.38–7.15$ (m, 10H), 4.94 (dd, 1H, $J = 7.7, 6.5$ Hz), 4.77 (ddt, 1H, $J = 9.1$, 7.7, 3.3 Hz), 4.44 (d, 1H, $J = 12.0$ Hz), 4.40 (d, 1H, $J = 12.0$ Hz), 4.18 (dd, 1H, $J = 8.8$, 7.7 Hz), 4.12 (dd, 1H, $J = 8.8$, 3.3 Hz), 3.74–3.66 (m, 2H), 3.35 (dd, 1H, $J = 9.2$, 7.3 Hz), 3.15 (dd, 1H, $J = 13.4$, 3.3 Hz), 2.72 (dd, 1H, $J = 13.4$, 9.1 Hz), 2.03–1.89 (m, 2H), 1.74–1.61 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H), 1.14 (s, 3H), 0.94 (t, 9H, $J = 8.0$ Hz), 0.67–0.56 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 176.7$, 152.5, 138.5, 135.6, 129.4, 128.8, 128.1, 127.5, 127.2, 127.1, 84.3, 80.1, 77.2, 73.2, 73.0, 66.1, 57.3, 48.7, 37.8, 36.3, 26.0, 20.5, 20.1, 19.4, 6.9, 5.2. **21**: colorless oil, IR (NaCl): 3070, 2961, 2858, 1732, 1473, 1112, 825, 740, 702. MS (EI, 85 °C) *m*/*z* (rel. intensity): 487 ($M-^t$Bu, 25.7), 395 (90), 331 (12), 269 (21), 239 (26), 199 (59), 139 (62), 91 (100). MS (ESI) *m*/*z*: 567 ($M+Na^+$), HRMS (EI) calcd for $C_{30}H_{35}O_4Si$ ($M-^t$Bu)$^+$: 487.2305, found: 487.2306. ^1H NMR (400 MHz, $CDCl_3 = 7.26$ ppm): $\delta = 7.75–7.65$ (m, 4H), 7.46–7.28 (m, 11H), 4.59 (d, 1H, $J = 11.8$ Hz), 4.54 (d, 1H, $J = 11.8$ Hz), 4.47 (d, 1H, $J = 18.9$ Hz), 4.42 (d, 1H, $J = 18.9$ Hz), 4.09 (dd, 1H, $J = 9.8$, 5.6 Hz), 3.55 (d, 1H, $J = 9.5$ Hz), 3.30 (d, 1H, $J = 9.5$ Hz), 2.20–2.12 (m, 1H), 1.86–1.76 (m, 2H), 1.63–1.51 (m, 1H), 1.34 (s, 3H), 1.06 (s, 9H), 0.90 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3 = 77.0$ ppm): $\delta = 212.5$, 137.4, 135.6, 133.6, 129.6, 128.4 127.9, 127.8, 127.6, 87.6, 84.8, 73.1, 71.3, 70.2, 38.6, 35.3, 26.9, 25.8, 24.5, 20.9, 19.4. **22**: colorless crystals, mp = 30–35 °C, MS (ESI) *m*/*z*: 1129 ($M+Na^+$), HRMS (CI) calcd for $C_{68}H_{90}O_9Si_2$ (M^+): 1106.6123, found: 1106.6049. $[\alpha]_D^{23}$ +6.6 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta = 7.71–7.60$ (m, 6H), 7.44–7.15 (m, 14H), 4.70 (d, 1H, $J = 11.6$ Hz), 4.70 (d, 1H, $J = 1.6$ Hz), 4.68–4.65 (m, 2H), 4.58 (d, 1H, $J = 11.3$ Hz), 4.48 (d, 1H, $J = 11.3$ Hz), 4.29 (d, 1H, $J = 11.6$ Hz), 4.17 (dd, 1H, $J = 9.4$, 6.2 Hz), 3.92 (ddd, 1H, $J = 9.8$, 8.6, 1.6 Hz), 3.71 (dd, 1H, $J = 6.5$, 2.3 Hz), 3.65–3.50 (m, 1H), 3.57 (dd, 1H, $J = 9.5$ Hz), 3.53 (d, 1H, $J = 9.5$ Hz), 3.46 (dd, 1H, $J = 9.7$, 6.9 Hz), 3.22 (d, 1H, $J = 9.5$ Hz), 3.10 (s, 3H), 2.14–1.85 (m, 4H), 1.83–1.70 (m, 1H), 1.53–1.38 (m, 5H), 1.23–1.10 (m, 1H), 1.04 (s, 9H), 1.03 (s, 9H), 0.86 (d, 3H, $J = 6.7$ Hz), 0.77 (d, 3H, $J = 6.6$ Hz), 0.81 (s, 3H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3 = 77.0$ ppm): $\delta = 212.4$, 138.7, 137.0, 2×133.7, 133.6, 133.4, 4×135.6, 4×135.5, 2×129.6, 2×129.5, 2×128.8, 2×128.3, 2×128.2, 127.9, 6×127.6, 4×127.5, 127.3, 98.1, 88.1, 81.9, 80.1, 79.4, 78.2, 75.2, 72.9, 71.9, 70.3, 66.8, 55.7, 38.2, 37.5, 36.2, 34.5, 33.3, 26.9, 26.8, 25.2, 24.1, 22.6, 20.8, 2×19.2, 15.4, 11.3.
18. The relative stereochemistry at C-7 to C-9 in adduct **22** was determined after 8,10-*syn* reduction of the keto group followed by protection of the 8,10-diol as the corresponding acetonide. H,H-Coupling constants in the six-membered ring and NOE-correlations served as diagnostic tools for this purpose.
19. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
20. Hoffmann, R. W. *Angew. Chem.* **2000**, *112*, 2134–2150.
21. (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157; (b) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodmann, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439–4458.