HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 167 - 172. © The Japan Institute of Heterocyclic Chemistry
Received, 10th April, 2008, Accepted, 15th May, 2008, Published online, 19th May, 2008.
DOI: 10.3987/COM-08-S(F)11

ENANTIOSELECTIVE SYNTHESIS OF A 3,5,5-TRIALKYLATED TETRONIC ACID DERIVATIVE‡

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Abstract – A convenient and enantioselective method for the synthesis of 3,5,5-trialkylated tetronic acid has been developed. The Dieckmann-type condensation of enantioenriched α-acyloxy-α,α-dialkylated acetic acid ester (**11**) proceeded in the presence of lithium hexamethyldisilazide, providing the expected tetronic acid derivative (**12**) after quenching with methoxymethyl chloride. The product (**12**) was converted into a doubly prenylated tetronic acid derivative (**13**), which constitutes a substructure of perforatumone, a newly isolated polycyclic polyprenylated acylphloroglucinol-type natural product.

3,5,5-Trialkylated tetronic acids depicted by the general structures (**1** and **2)** (Figure 1) are abundantly found in nature, and many of them exhibit a wide range of biological properties such as antimicrobial, antitumor, anticoagulant, antiepileptic, antifungal, insecticidal, analgesic, and anti-inflammatory activities.[1] Densely functionalized polyprenylated tetronic acids have recently been isolated from plants, especially those found in the family of Guttiferae. The research group of the Kao Corporation isolated two polyprenylated tetronic acids, erectumins A and B (**3**), from *Hypericum erectum* (Guttiferae) as a vasodilator and a skin medicine, respectively, for external use.[2] A more structurally functionalized tetronic acid-based compound, perforatumone (**4**), was recently isolated from the aerial part of *Hypericum perforatum* (St. John's wort) by Harrison and co-workers.[3] This natural product (**4)** is regarded to be a structural variant of polycyclic polyprenylated acylphloroglucinols (PPAPs), a representative of which is the antidepressant hyperforin.[4] The structure of **4** was characterized by its rare

‡ This paper is dedicated to Professor Emeritus Keiichiro Fukumoto, with respect and admiration, on the occasion of his 75th birthday.

7-oxabicyclo[4.2.1]nonane-8,9-dione skeleton. In recent years, a number of research groups have focused on the chemical synthesis of PPAPs because of their synthetically formidable structures and wide variety of biological activities.[5] To date, only one synthetic attempt on **4** has been reported.[6] We have been involved in the enantioselective total synthesis of **4**, and our initial efforts in this area have focused on the practical synthesis of 3,5,5-trialkylated tetronic acids as advanced synthetic intermediates toward **4**. Herein, we describe the enantioselective synthesis of an *O*-protected 3,5,5-trisubstituted tetronic acid derivative such as **13**, featured by the Sharpless asymmetric epoxidation protocol to introduce the C-5 chirality and also by Dieckmann-type condensation to form the tetronic acid skeleton.

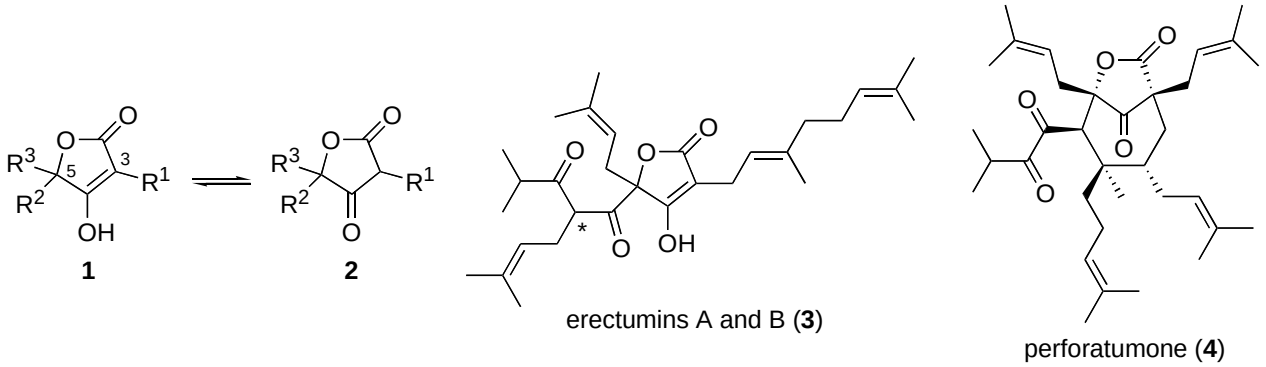


Figure 1. Structures of tetronic acids and related natural products **3** and **4**

Although a number of synthetic approaches toward functionalized tetronic acids have been reported,[7] we envisioned that the tetronic acid equivalent of **4**, simplified as structural formula (**A**) in Figure 2, would be synthesized via the Dieckmann-type condensation[8] of α-acyloxy-α,α-dialkylated acetic acid ester (**B**) and the subsequent exchange of the allyl groups at C3 and C5 for prenyl groups by cross-metathesis. This ester (**B**) for the attempted Dieckmann-type reaction, in turn, could be prepared from an enantioenriched α,α-differentially substituted chiral epoxide (**C**) through the epoxy-ring opening with a vinyl nucleophile, oxidation of one hydroxymethyl group into a methoxycarbonyl group, and acylation of the resulting tertiary alcohol with 4-pentenoic acid.

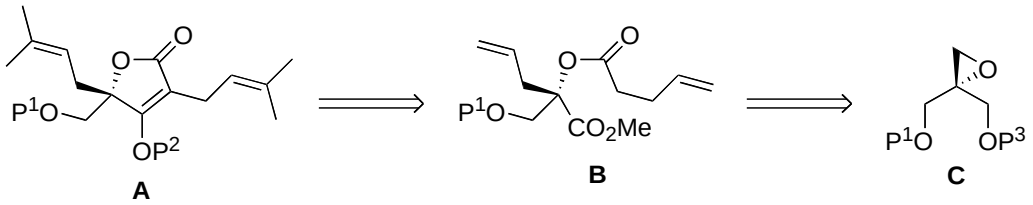
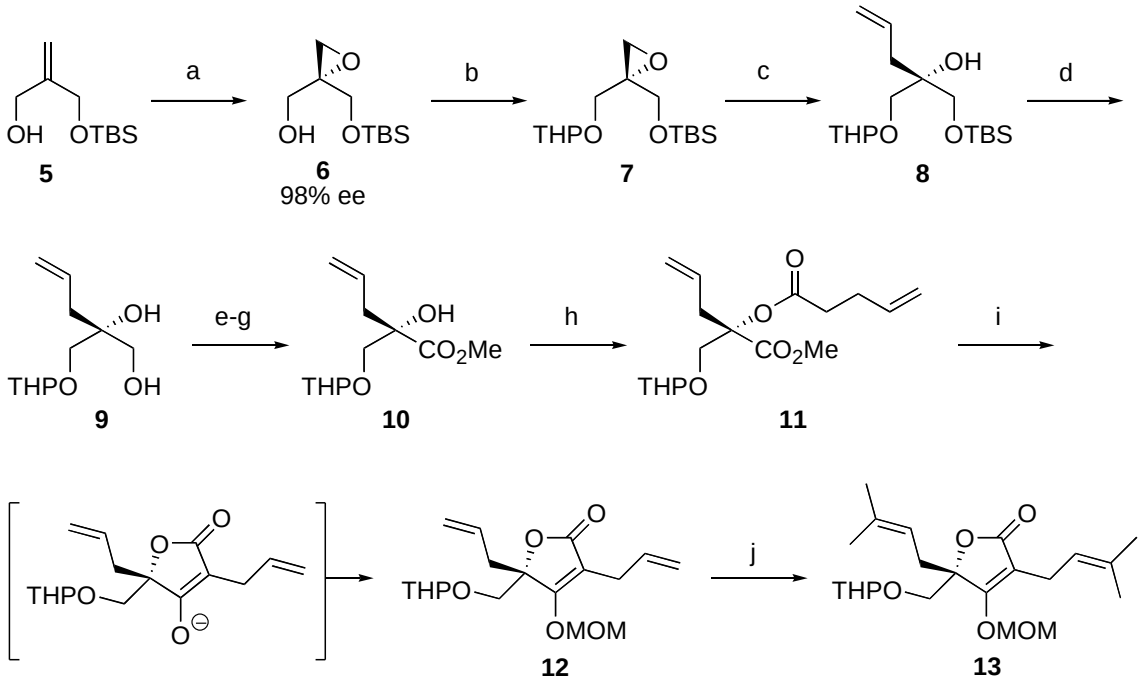


Figure 2. Our synthetic strategy for 3,5,5-trialkylated tetronic acids

The synthesis of **13** began with the Sharpless asymmetric epoxidation of known allylic alcohol (**5**)[9] (Scheme 1). Treatment of **5** with *tert*-butyl hydroperoxide in the presence of catalytic amounts of (–)-diisopropyl tartrate (DIPT) (10 mol %) and titanium tetraisopropoxide (8 mol %) provided α,α-disubstituted epoxide (**6**)[10,11] in high yield and excellent enantiomeric excess (98% ee).[12] The hydroxy

group in **6** was protected as tetrahydropyranyl (THP) ether, providing **7**. The epoxy-ring opening of **7** with vinylmagnesium bromide in the presence of copper iodide occurred regioselectively to furnish homoallylic alcohol (**8**) as a single product.[13] To minimize halohydrin formation and to maintain a high-yielding reaction, it was essential to use freshly prepared Grignard reagent. Removal of the *tert*-butyldimethysilyl (TBS) group in **8** provided diol (**9**), which was converted into hydroxy-ester (**10**) by two-step oxidation and the subsequent esterification of the resulting α,α-disubstituted glycolic acid. Acylation of the tertiary hydroxy group in **10** was well achieved by using sodium bis(trimethylsilyl)amide (NaHMDS) (1.2 equiv) and 4-pentenoyl chloride (1.5 equiv) to provide acyloxy-ester (**11**) in 70% yield and 28% of **10** was recovered. When *tert*-butyllithium or lithium bis(trimethylsilyl)amide (LiHMDS) was used as the base, the yield of **11** diminished significantly (47% or 39%). To produce the desired tetronic acid derivative, the Dieckmann-type condensation of **11** was executed by treatment with LiHMDS (1.5 equiv).[8] Trapping the intermediary enolate with methoxymethyl chloride (MOMCl) led to the corresponding MOM enol ether (**12**) in a good yield of 88%.[14] The two allyl groups in **12** were simultaneously exchanged with both prenyl groups by the cross-metathesis of **12** with 2-methyl-2-butene[15] using the second-generation Grubbs catalyst[16] to afford **13** in almost quantitative yield.[17]



Reagents and conditions: a) (–)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuO$_2$H, molecular sieves 4A, CH_2Cl_2, –20 °C, 91%; b) 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2, 85%; c) CH_2=CHMgBr, CuI, THF, –20 °C, 81%; d) *n*-Bu_4NF, THF, 96%; e) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O; g) MeI, $NaHCO_3$, DMF, 66% from **9**; h) NaHMDS, 4-pentenoyl chloride, THF, –78 °C to rt, 70% for **11** and 28% for recovered **10**; i) LiHMDS, THF, –78 °C to rt, then MOMCl, 88%; j) 2nd Grubbs catalyst, 2-methyl-2-butene, CH_2Cl_2, 99%.

Scheme 1

In conclusion, we have developed a novel method for the enantioselective synthesis of a 3,5,5-trialkylated tetronic acid derivative such as **13**. The present approach realizes access to the tetronic acid moiety of perforatumone (**4**). Further studies toward the total synthesis of **4** are in progress in this laboratory.

ACKNOWLEDGEMENTS

K. Takao thanks the Amano Institute of Technology for financial support.

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11. All new compounds were fully characterized by spectroscopic means [^{1}H NMR (300 MHz in $CDCl_3$), ^{13}C NMR (68 MHz in $CDCl_3$), and IR] and gave satisfactory HRMS (EI). Yields refer to homogeneous samples purified by chromatography on silica gel.
12. The *ee* value of **6** was determined by chiral HPLC analysis of the benzoyl ester derived from **6** (column, Daicel Chiralpak AD-H, 2-propanol: hexane = 1:400, flow rate = 0.5 mL/min; t_R = 29.9 min for benzoate of **6**, 25.8 min for the enantiomer).
13. Treatment of **6** with vinylmagnesium bromide and copper iodide produced a significant amount of the corresponding bromohydrin, formed by the ring opening with a bromide ion. The desired homoallylic alcohol was rather insufficiently obtained. This issue was avoided by the protection of

the primary hydroxy group.

14. Synthesis of **12**: To a cooled (–78 °C) stirred solution of **11** (1.25 g, 3.83 mmol) in THF (80 mL) was added dropwise LiHMDS (1.0 M solution in THF, 5.7 mL, 5.7 mmol). The mixture was stirred at –78 °C for 2 h, warmed to room temperature, and stirred for an additional 2.5 h. Then MOMCl (0.73 mL, 9.6 mmol) was added at 0 °C. The mixture was stirred for 2 h, diluted with brine (50 mL), and extracted with Et_2O (30 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc: hexane, 1:20) to provide 1.14 g (88%) of **12** (as a mixture of diastereomers regarding the asymmetric carbon in the THP group), and 114 mg (8%) of **11** was recovered. Compound **12** was obtained as white crystals: mp 61-63 °C TLC R_f 0.48 (EtOAc: hexane, 2:3); $[\alpha]_D^{21}$ + 30.4 (*c* 0.985, $CHCl_3$); IR 2945, 1755, 1665 cm^{-1}; ^1H NMR δ 1.42-1.80 (m, 6H), 2.39-2.71 (m, 2H), 3.13-3.18 (m, 2H), 3.46-3.56 (m, 1H), 3.50 (s, 3H × 1/2), 3.51 (s, 3H × 1/2), 3.52 (d, 1H × 1/2, *J* = 11.0 Hz), 3.67 (d, 1H × 1/2, *J* = 11.0 Hz), 3.74-3.85 (m, 1H), 3.89 (d, 1H × 1/2, *J* = 11.0 Hz), 3.97 (d, 1H × 1/2, *J* = 11.0 Hz), 4.59-4.69 (m, 1H), 5.01-5.30 (m, 6H), 5.61-5.77 (m, 1H), 5.85-5.99 (m, 1H); ^{13}C NMR δ 18.3 × 1/2, 19.2 × 1/2, 25.2, 26.7, 30.1 × 1/2, 30.2 × 1/2, 39.6 × 1/2, 37.0 × 1/2, 57.0, 61.2 × 1/2, 62.3 × 1/2, 67.8 × 1/2, 68.4 × 1/2, 84.6 × 1/2, 84.7 × 1/2, 95.4, 97.6 × 1/2, 99.9 × 1/2, 102.0, 115.2, 119.8 × 1/2, 119.9 × 1/2, 129.9 × 1/2, 130.0 × 1/2, 135.8, 170.7, 173.3 × 1/2, 173.4 × 1/2; HRMS calcd for $C_{18}H_{26}O_6$ (M^+) *m/z* 338.1729, found 338.1731.
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17. Synthesis of **13**: To a stirred solution of **12** (1.18 g, 3.50 mmol) in 2-methyl-2-butene (18 mL) was added a solution of the second-generation Grubbs catalyst (122 mg, 0.144 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred for 22 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc: hexane, 1:20) to provide 1.36 g (99%) of **13** as a colorless oil (a mixture of diastereomers regarding the asymmetric carbon in the THP group): TLC R_f 0.51 (EtOAc: hexane, 1:2); $[\alpha]_D^{21}$ + 1.8 (*c* 1.04, $CHCl_3$); IR 2940, 1755, 1665 cm^{-1}; ^1H NMR δ 1.60 (s, 6H), 1.67 (s, 6H), 1.40-1.80 (m, 6H), 2.29-2.64 (m, 2H), 3.07 (d, 2H, *J* = 6.0 Hz), 3.46-3.55 (m, 1H), 3.49 (s, 3H × 1/2), 3.51 (s, 3H × 1/2), 3.53 (d, 1H × 1/2, *J* = 10.8 Hz), 3.67 (d, 1H × 1/2, *J* = 10.8 Hz), 3.74-3.91 (m, 1H), 3.87 (d, 1H × 1/2, *J* = 10.8 Hz), 3.94 (d, 1H × 1/2, *J* = 10.8 Hz), 4.59-4.68 (m, 1H), 4.95-5.04 (m, 2H), 5.14-5.24 (m, 2H); ^{13}C NMR δ 17.7, 17.9, 18.3 × 1/2, 19.1 × 1/2, 21.9, 25.3, 25.5, 25.8, 30.2, 31.0 × 1/2, 31.1 × 1/2, 56.8 × 1/2, 56.9 × 1/2, 61.2 × 1/2, 62.0 × 1/2, 68.0 × 1/2, 68.4 × 1/2, 85.2 × 1/2, 85.4 × 1/2, 95.4, 97.5 × 1/2, 99.3 × 1/2, 104.6 × 1/2, 104.7 × 1/2, 115.5 ×

1/2, 115.6 × 1/2, 122.3 × 1/2, 122.4 × 1/2, 132.1 × 1/2, 132.2 × 1/2, 136.1 × 1/2, 136.2 × 1/2, 169.5, 173.7 × 1/2, 173.8 × 1/2; HRMS calcd for $C_{22}H_{34}O_6$ (M^+) *m/z* 394.2355, found 394.2350.