Efficient Synthesis of (−)-*trans*-Kumausyne via Tandem Intramolecular Alkoxycarbonylation−Lactonization

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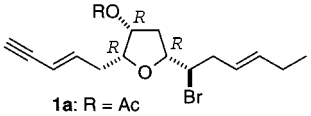
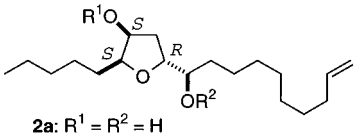
The red algal metabolites *trans*-kumausyne (**1a**) and deacetylkumausyne (**1b**),[1] by virtue of their unusual all-*cis* 3-oxygenated-2,5-dialkyltetrahydrofuran core and rich functionality, have been the object of considerable synthetic effort.[2] Overman's group accomplished the landmark total synthesis of (±)-**1a** in 18 steps from 2-cyclopentylidenecyclopentanone using a novel Prins cyclization−pinacol rearrangement for elaborating the tetrahydrofuran (THF) core.[3] During the course of our work,[4] Sugimura reported an enantioselective synthesis of **1a** from L-arabinose (19 steps, 1.1% overall yield) in which the THF ring is formed by cyclization of a β-silyl cation.[5] More recently, Martín disclosed a 22-step synthesis of (−)-**1b** from propargyl alcohol that employs brominative cyclization as the key step.[6] Prompted by these reports, we describe here a considerably shorter and simpler synthesis of (−)-*trans*-kumausyne by a potentially general pathway that we expect to extend in due course to the preparation of brown algal metabolites (e.g., **2a**−**c**) that possess a 2*S*,3*S*,5*R* 3-oxygenated-2,5-dialkyltetrahydrofuran core.[7]



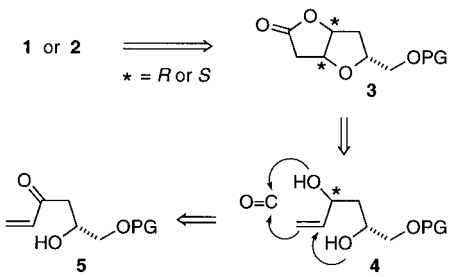
1a: R = Ac
1b: R = H



2a: $R^1 = R^2 = H$
2b: $R^1 = H$, $R^2 = CO\text{-}n\text{-}C_{15}H_{31}$
2c: $R^1 = n\text{-}C_{15}H_{31}CO$, $R^2 = H$

Retrosynthetic analysis dictated by considerations of atom-economy and stereochemical flexibility suggested that both **1a** and **2a**, as well as their congeners, should be available by a unified strategy based upon tandem intramolecular alkoxycarbonylation−lactonization[8] for assemblage

Scheme 1



of the THF unit (cf. **4** → **3**, Scheme 1). Either diastereoisomer of diol **4** (2*R*,4*R* or 2*R*,4*S*) should be accessible at will from the same ketone (**5**) by stereoselective reduction under the appropriate conditions.[9]

Our approach began with the selective reduction[10] of dimethyl (*R*)-malate (**6**) to the known diol **7**[11,12] (Scheme 2). Treatment of **7** with 1 equiv of *tert*-butyldiphenylsilyl chloride and imidazole in DMF at 0 °C accomplished selective protection of the primary alcohol group to furnish **8**[13] in 91% yield. Ester **8** was transformed into β-hydroxy enone **10** by recourse to Weinreb's method.[14] Thus, reaction of **8** with N,O-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum provided the crystalline *N*-methoxy-*N*-methylamide **9** (89%), which on exposure to vinylmagnesium bromide gave enone **10** in an unoptimized yield of 53%. This enone was subjected to reduction under the Evans protocol[9] ($Me_4NHB(OAc)_3$ in MeCN/AcOH) to afford the desired *anti*-diol **11** in 89% yield after silica gel chromatography. None of the *syn*-isomer of **11** could be detected in the ^{1}H NMR spectrum of the crude reduction product.[15]

With a supply of diol **11** in hand, the stage was now set for the crucial alkoxycarbonylation−lactonization. Treatment of **11** with carbon monoxide in the presence of $PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), and AcONa (4 equiv) in AcOH[8] afforded uniquely the bicyclic lactone[16] **12** in a yield of 93%. Crafting of the lactone ring into the requisite enyne and hydroxyl appendages was accomplished by DIBAL-H reduction and subsequent Wittig-olefination with the commercially available [3-(trimethylsilyl)-2-propynyl]triphenylphosphonium bromide.[17] In this manner, pure *trans*-enyne **13** was obtained in 85% yield after separation from its *cis*-isomer (8%) by flash chromatography. Next, **13** was con-

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(4) Presented in parts at the 211th ACS National Meeting, New Orleans, LA, March 24−28, 1996 (ORGN 434), and the 78th CSC Conference and Exhibition, Guelph, Ontario, May 28−June 1, 1995 (OR6: 338).

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(7) Barrow, R. A.; Capon, R. J. *Aust. J. Chem.* **1990**, *43*, 895−911.

(8) (a) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171−3174. (b) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 3207−3210.

(9) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741−750 and references therein.

(10) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067−4086.

(11) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400−10401.

(12) Yields refer to chromatographically purified products, characterized by high-field ^{1}H and ^{13}C NMR. The elemental composition of new compounds was confirmed by C,H-microanalyses or HRMS.

(13) Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Narisano, E.; Riva, R. *Tetrahedron* **1994**, *50*, 11967−11982. See also: Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holtzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545−2548.

(14) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (b) For an excellent review see: Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15−40.

(15) Diol **11** was readily distinguished by NMR from its *syn*-isomer (*R*,*R*); the latter was prepared by reduction of **10** with $NaBH_4$ in the presence of Et_2BOMe (cf. ref 9).

(16) A substantially longer route to lactone **12** from L-arabinose (12 steps) and the transformation of **12** into (−)-**1a** and (−)-**1b** have been reported by Sugimura (ref 5).

(17) Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984**, *106*, 5734−5736. See also ref 5.

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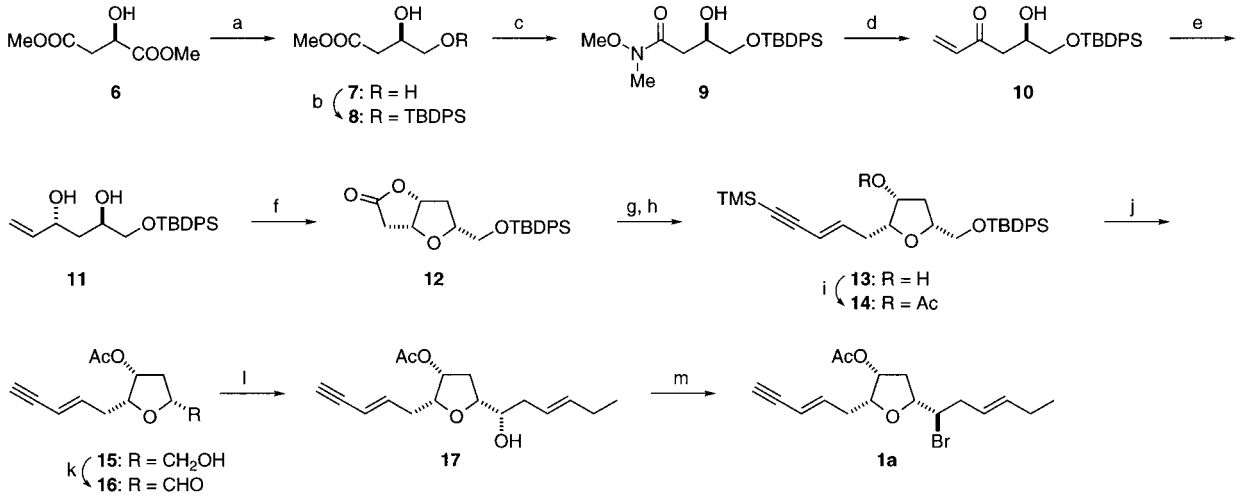
Scheme 2[a]



[a] Key: (a) $BH_3 \cdot Me_2S$, $NaBH_4$, THF, rt (87%); (b) TBDPSCl (1 equiv), imidazole, DMF, 0 °C (91%); (c) (MeO)MeNH·HCl, $AlMe_3$, CH_2Cl_2, 40 °C (89%); (d) CH_2=CHMgBr, THF, 20 → 50 °C (53%); (e) $Me_4NHB(OAc)_3$, MeCN−AcOH, −40 °C (89%); (f) CO, $PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (4 equiv), AcOH, rt (93%); (g) DIBAL-H (1.5 equiv), THF, −78 °C (100%); (h) TMSC≡$CCH_2P^+Ph_3Br^-$ (2 equiv), *t*-BuOK, Et_2O, rt (85%); (i) Ac_2O, DMAP, pyridine, rt (100%); (j) $PhCH_2NMe_3F \cdot xH_2O$, MeCN, 0 → 25 °C (95%); (k) Swern oxidation (96%); (l) (CH_2=CH)CH(TMS)Et, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 → +25 °C (52%); (m) CBr_4, *n*-Oct_3P, toluene, 80 °C (50%).

verted to the acetate **14** in quantitative yield. Removal of both silyl protecting groups of **14** was best achieved (95% yield) by using benzyltrimethylammonium fluoride hydrate[18] in acetonitrile. Swern oxidation of the resulting alcohol **15** afforded aldehyde **16** with high efficiency. Elaboration of the *trans*-1-bromo-3-hexenyl side chain was carried out in a fashion similar to that described by Overman.[3] Thus, Sakurai reaction of aldehyde **16** with 3-(trimethylsilyl)-1-pentene[3] provided alcohol **17** as the sole isomer in 52% yield. Treatment of this alcohol with CBr_4 and tri-*n*-octylphosphine in toluene[19] at 80 °C afforded (−)-*trans*-kumausyne (**1a**, 50%), whose optical rotation [$[\alpha]^{26}_D$ −2.9° (*c* 0.11, $CHCl_3$) [lit.[1] $[\alpha]^{26}_D$ −2.3° (*c* 0.62, $CHCl_3$)]] and spectral properties (^1H and ^{13}C NMR, and IR) were consistent with those reported in the literature.[1,3]

In summary, we have achieved an exceptionally concise and efficient synthesis of (−)-*trans*-kumausyne[20] from dimethyl (*R*)-malate (13 steps, 6.2% overall yield), which demonstrates the serviceability of the general plan outlined in Scheme 1 for stereocontrolled construction of 3-oxygenated 2,5-dialkyltetrahydrofurans. In addition, this work serves to highlight the intrinsic power of tandem intramolecular alkoxycarbonylation−lactonization for building complexity rapidly, in atom-economical fashion. Further applications of this strategy to the synthesis of structurally related natural products are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **8**−**17** and **1a** (11 pages).

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(18) This reagent proved superior to TBAF for deprotecting **14**; for similar observations see: Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910−3926.

(19) (a) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86−87. (b) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345−4348.

(20) After submission of this manuscript, a 22-step synthesis of (−)-*trans*-kumausyne from D-xylose, which employs radical cyclization of a β-alkoxyacrylate as the key step, was reported by Lee: Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S,; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757−7758.