Pergamon

Tetrahedron Letters, Vol. 36, No. 9, pp. 1487-1490, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00066-6

A Total Synthesis of (+)-Eremantholide A

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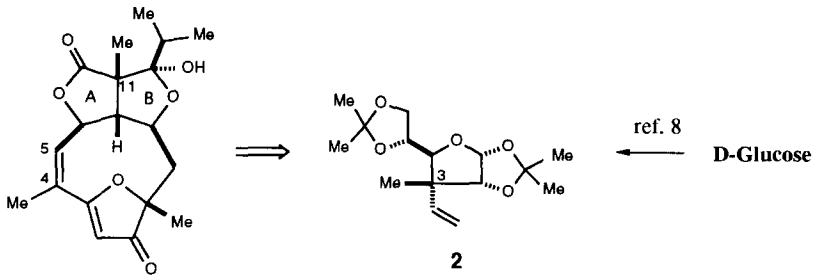
Abstract: Stereoselective and enantiospecific total synthesis of (+)-eremantholide A (**1**) is described. The present total synthesis features 1) regio- and stereoselective radical carbocyclization of D-glucose-derived γ-lactone **7**, and 2) a nine-membered ring formation by the coupling reaction of bicyclic triflate **18** and known furanone **19** followed by a vinylogous aldol reaction.

In 1975, Le Quesne and co-workers isolated a new furanoheliangolide sesquiterpene (+)-eremantholide A (**1**) (Fig. 1) from the stem parts of the Brazilian plant *Eremanthus elaeagnus* as an antitumor compound against cells derived from human carcinoma of the nasopharynx (KB) in vitro.[1-3] They also determined the structure and relative stereochemistry of **1** by means of spectroscopic studies and a single crystal X-ray analysis. The structural characteristics of this natural product **1** are 1) a 3,7-dioxabicyclo[3.3.0]octan-2-one substructure with five contiguous stereogenic centers (the A/B ring system), and 2) a highly strained nine-membered ring containing the endocyclic C4-C5 double bond, a part of which shares a 2,2,5-trisubstituted 3(2*H*)-furanone ring. Owing to this structural novelty and its antitumor property, compound **1** is a challenging target for total synthesis in several groups.[4,5] Recently, Boeckman and co-workers completed the first total synthesis of (+)-eremantholide A establishing the speculated absolute stereochemistry of the natural form (**1**).[6,7] Herein, we disclose our total synthesis of **1** which was achieved in a completely different approach starting from the D-glucose-derived synthon **2** as shown in Fig. 1.[8,9] The quaternary carbon center (C3) in **2** was eventually altered to C11 of **1**.

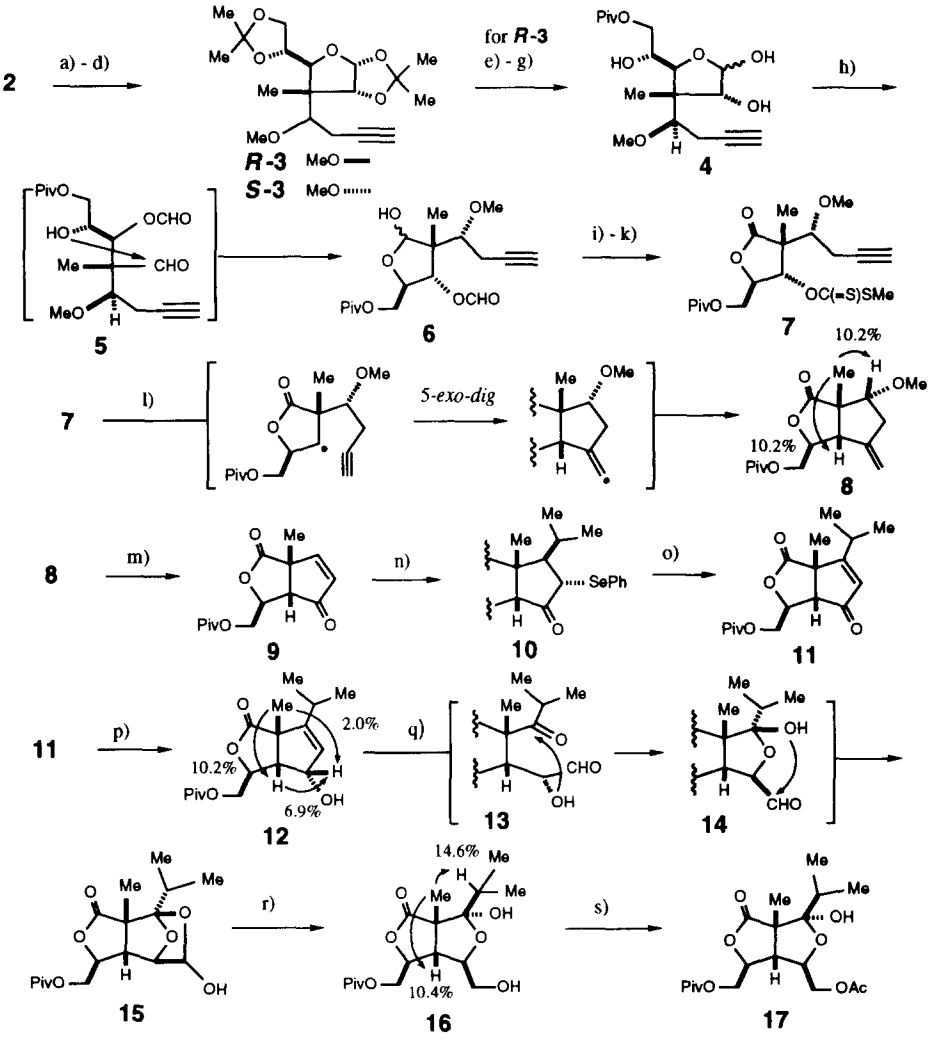


(+)- Eremantholide A 1 **2**

Fig. 1

First, we explored the stereoselective access to a suitably protected form of the A/B ring equivalent, i.e., compound **16**. The synthesis of **16** starting from **2** is summarized in Scheme 1.[10] A four-step functional group transformation of the vinyl group in **2** installed a protected 3-butyn-1-ol functionality at C3 of **2**, providing a 6:1 diastereomeric mixture of ***R*-3** and ***S*-3**. The major product ***R*-3**, of which stereochemistry was

confirmed by the n. O. e. difference experiment of the advanced bicyclic derivative **8**, was converted to a partially protected hemiacetal mixture **4** by a 3-step reaction. Glycol cleavage of **4**, which followed a spontaneous ring-closure of thus formed aldehyde **5**, provided an anomeric mixture **6** of a C2 branched pentofuranose. A 3-step reaction from the mixture **6** provided xanthate ester **7**. We utilized a radical ring closure strategy using the xanthate **7** to give a precursor for the B-ring construction, i. e., compound **8**. As anticipated, the radical cyclization proceeded regio- (5-*exo*-dig) and stereoselectively (cis-fused) in high yield under standard conditions.

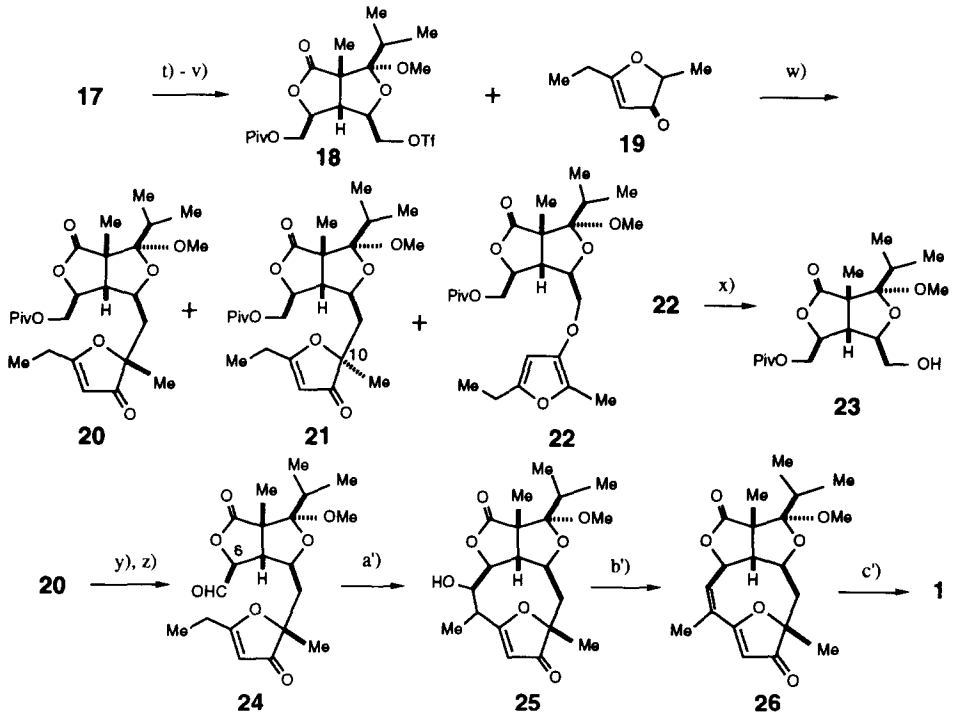


Reagents and conditions: a) O_3 / CH_2Cl_2 / -78 °C, then Ph_3P (89%); b) 1-trimethylsilylpropyne / *n*-BuLi / THF / -78 °C (83%); c) *n*-Bu_4NF / THF / -15° C (93%); d) NaH / DMF / rt, then MeI (***R*-3**, 83%; ***S*-3** 14%); e) 60% aq. AcOH / rt; f) PivCl / pyr. / rt (98% for 2 steps); g) 60% aq. CF_3COOH / rt (66%, 17% recovery of the 1,2-*O*-isopropylidene deriv.); h) $NaIO_4$ / aq. MeOH / rt; i) PCC / CH_2Cl_2 / MS 4A / rt; j) Et_3N / MeOH / rt (88% for 3 steps); k) NaH / imidazole / THF; CS_2 / -15 °C; then MeI (95%); l) *n*-Bu_3SnH / AIBN / toluene (0.01 M solution) / reflux (87%); m) 1) O_3 / CH_2Cl_2 / -78°C; then Ph_3P, 2) DBU / benzene / reflux (84% for 2 steps); n) CuBr•Me_2S / *i*-PrMgBr / THF / -78 °C, then PhSeCl (89%); o) $NaIO_4$ / $NaHCO_3$ / aq. MeOH / rt (83%); p) $NaBH_4$ / $CeCl_3$•$7H_2O$ / MeOH / -15 °C (97%); q) O_3 / CH_2Cl_2 / -78 °C, then Ph_3P (93%); r) $NaBH_4$ / MeOH / -15 °C; s) Ac_2O / pyr. / rt (90% for 2 steps).

Scheme 1

Neither the cyclization product formed via a 6-*endo*-dig mode nor the deoxygenation product was found. This highly efficient radical-mediated ring closure, which affords the desired bicyclic compound **8** exclusively, should be worth to mention.[11] Ozonolysis of **8** followed by DBU-catalyzed β-elimination of the methoxy group provided a cyclopentenone derivative, i.e., compound **9**. 1,4-Conjugate addition of an isopropyl anion onto the enone system in **9** followed by trapping of the resulting enolate with phenylselenenyl group afforded **10**, from which the cyclopentenone system was regenerated by oxidative elimination of the selenenyl group. The keto carbonyl in thus formed **11** was then reduced stereoselectively by Luche's conditions[12] to give a bicyclic cyclopentenol **12**. The hydride delivery occurred from the less hindered convex face. Ozonolysis of **12** and reductive workup afforded a tricyclic lactone **15** as a hemiacetal mixture, which was treated with $NaBH_4$ to give the 3,7-dioxabicyclo[3.3.0]octan-2-one **16**. The formation of **15** from **12** is explainable via intermediates **13** and **14**. The stereochemistries of **8**, **12** and **16** were verified by their n. O. e. difference experiments (see Scheme 1). Compound **16** and its acetate **17** were expected to be synthetic equivalents to the A/B ring of **1**.

Next, we investigated the coupling of the A/B ring, i. e., the triflate **18** derived from **17**, and 5-ethyl-2-methyl-3(2*H*)-furanone (**19**)[13] (Scheme 2). After thorough screening of the bases and solvents, we found that sodium bis(trimethylsilyl)amide (NaHMDS) was most effective base which gave the desired *C*-alkylation product **20** as the major diastereomer.[14,15] The *O*-alkylation product **22** accompanied significantly. Acid hydrolysis of **22** regenerated the A/B ring unit **23** efficiently , which can be reusable for the coupling reaction.



Reagents and conditions: t) $CH(OMe)_3$ / PPTS / MeOH / reflux (89%); u) MeONa / MeOH / 0 °C (**23**, 92%); v) Tf_2O / Et_3N / CH_2Cl_2 / -78 °C; w) NaHMDS / 15-cr-5 / toluene / -78 °C (**20**:**21** = 4:1, 15% combined yield for 2 steps; **22**, 66%); x) *p*-TsOH / MeOH / 0 °C (95%); y) MeONa / MeOH / rt (83%); z) $(COCl)_2$ / DMSO / CH_2Cl_2 / -78 °C, then Et_3N; a') KHMDS / 18-cr-6 / THF / -78 °C (37% for 2 steps); b') 1) MsCl / 4-DMAP / pyr. (91%) 2) DBU / toluene / reflux (76%); c') 6 M aq. HCl / THF (1: 8) (83%).

Scheme 2

The final stage of our total synthesis was the crucial nine-membered ring formation by the intramolecular vinylogous aldol reaction of the substrate **24** prepared from **20**, which was separable from **21** and **22**. For this pivotal step, KHMDS was found to be most effective base, affording the aldol product **25** as a diastereomeric mixture. This reaction proceeded without epimerization of C6. Mesylation of the mixture **25** followed by DBU-catalyzed elimination provided **26**. Thus we could succeed the direct connection of intact furanone **19** to the A/B ring system. Finally, deblocking of the methyl acetal in **26** provided (+)-eremantholide A (**1**), [for synthetic **1**: mp 182-184 °C, and $[\alpha]^{26}_D$ +69.9 ° (*c* 0.10, EtOH); for natural **1**: mp 184-185 °C, and $[\alpha]^{28}_D$ +68.8° (*c* 0.18, EtOH)], which was identical with natural specimen (IR, ^{1}H NMR, and TLC mobility).

Acknowledgment: We are grateful to Professors Le Quesne (Northeastern Univ.) for sending us a sample of natural **1**, and to Boeckman (Univ. of Rochester) for their spectral data (IR and ^{1}H NMR) of synthetic **1** and a synthetic intermediate.

REFERENCES AND NOTES

1. Raffauf, R. F.; Huang, P.-K. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F. *J. Am. Chem. Soc.* **1975,** *97,* 6884.
2. Le Quesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1,* **1978,** 1572.
3. Herz, W.; Kumar, N.; Vichnewski, W.; Blount, J. F. *J. Org. Chem.* **1980,** *45,* 2503.
4. Tam, T. F.; Fraser-Reid, B. *J. Org. Chem.* **1980,** *45,* 1344.
5. McDougal, P. G.; Oh, Y.-I.; VanDerveer, D. *J. Org. Chem.* **1989,** *54,* 91.
6. Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991,** *113,* 9682.
7. Boeckman, R. K., Jr.; Heckendorn, D. K.; Chinn, R. L. *Tetrahedron Lett.* **1987,** *28,* 3551.
8. Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *Chem. Lett.* **1985,** 1925; *J. Org. Chem.* **1987,** *52,* 1201.
9. Natural products synthesis using **2**, see: Tadano, K. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 405-455.
10. All new compounds depicted in Schemes 1 and 2 were fully characterized by spectral means (IR, 270 MHz ^{1}H NMR) and combustion analysis and/or HRMS. Yields refer to purified compounds obtained by silica gel chromatography. Selected data are specified for **9**, **17**, **20**, and **26**; **9**: mp 42.5-44 °C; $[\alpha]^{26}_D$ -131.2° (*c* 0.66, $CHCl_3$); ^{1}H NMR δ 1.24 (s, 9 H), 1.65 (s, 3 H), 2.82 (d, *J* = 3.7 Hz, 1 H), 4.23 (dd, *J* = 4.4, 12.5 Hz, 1 H), 4.39 (dd, *J* = 3.7, 12.5 Hz, 1 H), 4.64 (dt, *J* = 4.4, 3.7 Hz, 1 H), 6.23 (d, *J* = 5.5 Hz, 1 H), 7.61 (d, *J* = 5.5 Hz, 1 H). **17**: $[\alpha]^{20}_D$ -15.0° (*c* 1.36, $CHCl_3$); ^{1}H NMR δ 1.02, 1.09 (2 d, each *J* = 7.0 Hz, 3 H x 2), 1.22 (s, 9 H), 1.39 (s, 3 H), 2.09 (s, 3 H), 2.11 (hept. *J* = 7.0 Hz, 1 H), 2.55 (dd, *J* = 3.7, 7.7 Hz, 1 H), 2.60 (s, 1 H), 4.10 (dd, *J* = 5.1, 11.4 Hz, 1 H), 4.14 (dd, *J* = 4.8, 12.5 Hz, 1 H), 4.18 (dd, *J* = 4.8, 11.4 Hz, 1 H), 4.27 (dd, *J* = 3.3, 12.5 Hz, 1 H), 4.35 (ddd, *J* = 3.7, 4.8, 5.1 Hz, 1 H), 4.72 (ddd, *J* = 3.3, 4.8, 7.7 Hz, 1 H). **20**: $[\alpha]^{27}_D$ -25.1° (*c* 0.75, $CHCl_3$); ^{1}H NMR δ 1.07, 1.08 (2 d, each *J* = 7.1 Hz, 3 H x 2), 1.23 (s, 9 H), 1.24 (t, *J* = 7.7 Hz, 3 H), 1.31, 1.40 (2 s, 3 H x 2), 2.00 (dd, *J* = 2.6, 14.3 Hz, 1 H), 2.08 (hept, *J* = 7.1 Hz, 1 H), 2.19 (dd, *J* = 10.6, 14.3 Hz, 1 H), 2.23 (dd, *J* = 4.0, 7.0 Hz, 1 H), 2.52 (q, *J* = 7.7 Hz, 2 H), 3.24 (s, 3 H), 3.98 (ddd, *J* = 2.6, 4.0, 10.6 Hz, 1 H), 4.15 (d, *J* = 4.6 Hz, 2 H), 4.41 (dt, *J* = 7.0, 4.6 Hz, 1 H), 5.43 (s, 1 H). **26**: $[\alpha]^{26}_D$ +38.7 ° (*c* 0.13, $CHCl_3$); ^{1}H NMR δ 1.09, 1.12 (2 d, each *J* = 7.3 Hz, 3 H x 2), 1.30, 1.49 (2 s, 3 H x 2), 1.99-2.08 (m, 4 H), 2.10 (hept, *J* = 7.3 Hz, 1 H), 2.38 (dd, *J* = 2.6, 13.6 Hz, 1 H), 2.77 (dd, *J* = 4.0, 7.0 Hz, 1 H), 3.22 (s, 3 H), 3.73 (ddd, *J* = 2.6, 4.0, 11.7 Hz, 1 H), 4.73 (dt, *J* = 7.0, 2.2 Hz, 1 H), 5.60 (s, 1 H), 5.98-6.01 (m, 1 H).
11. A recent example of the carbocyclization of carbohydrate-templates by means of a radical ring closure, see: Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994,** *59,* 4048.
12. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981,** *103,* 5454.
13. Compound **19** was prepared according to a literature: Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta Chem. Scand., Ser. B* **1982,** *36,* 1.
14. The structure of **20** was confirmed by transformation of **20** into a Boeckman's synthetic intermediate.[6]
15. Interestingly, when the coupling reaction was carried out with LiHMDS in toluene at -78 ~ 0 °C, a mixture of another *C*-alkylation product **21** (the C10 epimer) and **20** was obtained in 81% combined yield, in which **21** was predominant (**20** : **21** = ca. 1 : 40). In this case, no *O*-alkylation product **22** was formed.

(*Received in Japan* 29 *September* 1994; *revised* 21 *November* 1994; *accepted* 27 *December* 1994)