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Tetrahedron Letters 45 (2004) 8843–8846
Tetrahedron Letters

A concise synthesis of the functionalized [5–7–6] tricyclic skeleton of guanacastepene A

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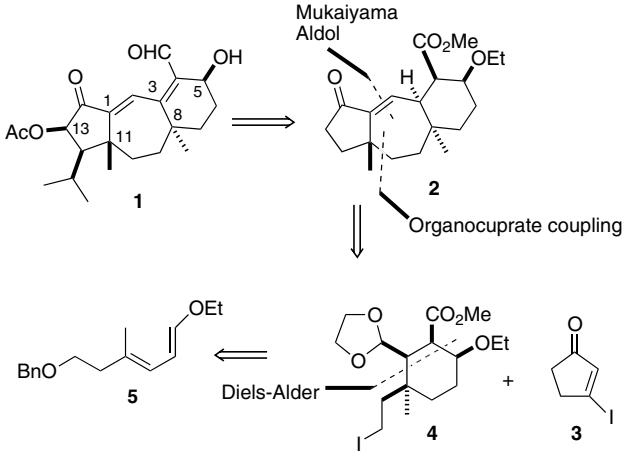
Received 9 September 2004; revised 28 September 2004; accepted 30 September 2004

Abstract—The six membered ring of guanacastepene A was constructed by a Diels–Alder reaction of 1,1,4-trisubstituted diene to set up the correct relative stereochemistry at the C8 quaternary center and the remote C5 stereocenter. In 10 efficient steps from the Diels–Alder adduct **9**, the desired highly functionalized [5–7–6] tricyclic skeleton **2** was synthesized. Key steps involve trimethylsilyl chloride (TMSCl) assisted Michael addition to form enol ether and the usage of the enol ether in the following intramolecular Mukaiyama aldol reaction to form the middle seven membered ring of guanacastepene A.

Guanacastepene A (**1**), isolated from a fungus growing on the tree *Daphnopsis Americana* by Clardy and co-workers, showed antibiotic activity against both methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Entercoccus faecalis* (VREF).[1] Later publication[2] showed that guanacastepene A also has hemolytic activity reducing its therapeutic potential as an antibiotic agent on its own. Nevertheless, efficient synthesis of guanacastepene A presents an opportunity for the production of its analogs that can be therapeutically useful. Structurally, guanacastepene A possesses interesting features such as a [5–7–6] fused tricyclic framework, a densely functionalized top half and a hydrophobic bottom half. The three stereocenters at C5, C8, and C11 that are separated by two methylene units from each other are challenging to set up. These structural challenges and the promising biological profile of guanacastepene A have made it an attractive synthetic target.[3] Danishefsky and co-workers reported the first and only total synthesis,[3f,3g] followed by Snider's[3c] and Hanna's[3t] formal total synthesis. Eleven more groups have disclosed various synthetic approaches to the bicyclic and tricyclic core structures of **1**. Our group also communicated a convergent approach to build a model [5–7–6] tricyclic core structure of guanacastepene A.[3u] In applying the basic reaction tools that were developed in our model studies, there remained many challenges associated with building the fully functionalized system **2** with C5 oxygenation and C8, C11 quaternary methyls in place (Scheme 1). To set the correct relative stereochemistry between C5 and C8 via intermolecular Diels–Alder reaction, we decided to employ 1,1,4-trisubstituted diene **5**.[4] Organocuprate coupling between β-iodocyclopentenone (**3**) and six-membered ring moiety **4** followed by Michael addition/intramolecular Mukaiyama aldol



Scheme 1. Retrosynthetic analysis for guanacastepene A.

Keywords: Guanacastepene A; [5–7–6] Tricycle; Intermolecular Diels–Alder reaction; A tandem Michael addition/intramolecular Mukaiyama aldol reaction.
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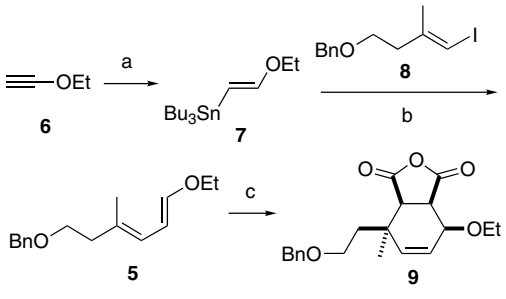
doi:10.1016/j.tetlet.2004.09.187

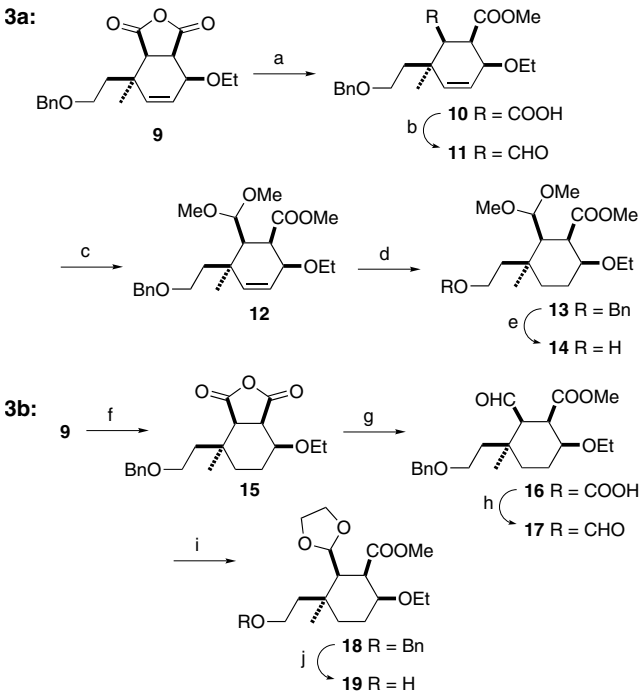
reaction was to provide the tricyclic structure **2**. The C12 isopropyl group and C13 acetoxy group can be introduced at a later stage from intermediate **2**. Herein, we report synthesis of the highly functionalized tricycle **2**.

The required diene **5** was synthesized in an efficient two-step process (Scheme 2). Hydrostannation of ethoxyacetylene (**6**) catalyzed by $Pd(PPh_3)_4$ generated the (β-*E*-ethoxyvinyl)tributyltin (**7**) as the major isomer. The minor α-isomer did not participate in the subsequent Stille reaction. Two known procedures[5] to prepare **7** were tried but brought inferior results. Stille coupling with benzyl-protected (*E*)-vinyl iodide **8**[6] applying Hibino's condition[7] was rapid and high yielding. The desired Diels–Alder reaction between the very sensitive diene **5** and maleic anhydride proceeded in 70% yield with exclusive *endo*-selectivity. The success of the reaction was dependent on the addition of hydroquinone and high purity of the diene.

Methanolysis of **9** was sluggish with a much lower yield compared to the model system lacking the C5 ethoxy and C8 methyl group, presumably due to rigidity of the ring and increased steric hindrance (Scheme 3). Functional group interchange of carboxylic acid **10** to aldehyde **11** and to acetal **12** proceeded smoothly in four steps. Hydrogenation to simultaneously remove the double bond and benzyl group failed with 10% Pd/C and a variety of other conditions. Hydrogenation of **12** with 5% Pd/C furnished compound **13**, which was difficult to characterize initially because a rapid conformational exchange between two conformers of **13** resulted in disappearance of proton and carbon signals in the NMR at room temperature. The structure of **13** was confirmed through variable temperature NMR experiments.[8] Hydrogenolysis of **13** was problematic due to reaction of the resulting hydroxyl group with the dimethyl acetal moiety to form a cyclic acetal. Sensitive alcohol **14** could be secured by adding a pH 7 buffer to the hydrogenation mixture. However, the formation of cyclic acetal was observed again upon the direct conversion of the hydroxy group in **14** to the corresponding iodide. Two step approach, mesylation followed by the Finkelstein reaction, failed as well. These difficulties led us to develop the improved sequence of reactions shown in Scheme 3b.



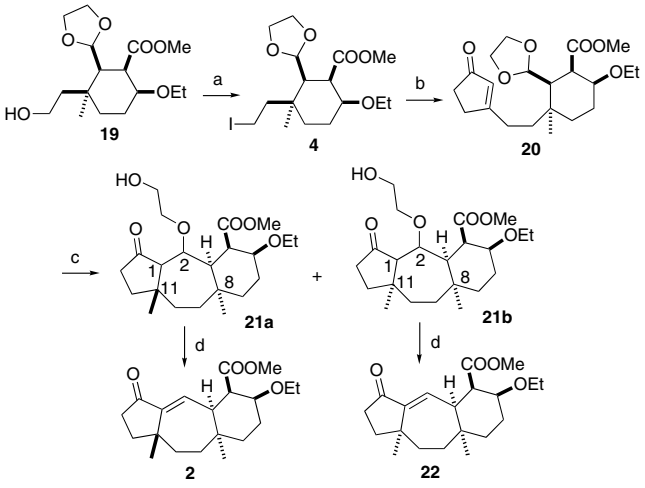
Scheme 2. Reagents and conditions: (a) Bu_3SnH, $Pd(PPh_3)_4$, CH_2Cl_2, 5 h, 92%, β-*E*–α 1.0:0.6; (b) $Pd(PPh_3)_2Cl_2$ (0.05 equiv), Et_4NCl (1 equiv), DMF, 80 °C, 2 h, 83%; (c) maleic anhydride (3 equiv), hydroquinone (0.023 equiv), benzene (degassed, 0.4 M of **5**), pressure tube, 105 °C, 3.5 d, 70%.



Scheme 3. Reagents and conditions: (a) MeOH, 80 °C, 3 d, 51%; (b) (i) ClCOOEt, NMM, THF, 10 min, (ii) $NaBH_4$ (2 equiv), THF–MeOH = 1:1.3, 25 min, (iii) oxalyl chloride, DMSO, Et_3N, −60 °C, 30 min, 82% for three steps; (c) Bu_4NBr_3 (0.01 equiv), MeOH, $CH(OMe)_3$, 1.5 h, 90%; (d) H_2, 5% Pd/C (0.1 equiv), EtOAc, 81%; (e) H_2, $Pd(OH)_2$ (0.3 equiv), MeOH–buffer (pH = 7) 3:1, 17 h, quantitative; (f) H_2, 10% Pt/C (0.1 equiv), EtOAc, 92%; (g) MeOH, 80 °C, 46 h, 85%; (h) $BH_3{\cdot}Me_2S$ (1.1 equiv), rt to 40 °C, Et_2O/THF (5:1), 1 h, then PCC (2.5 equiv), CH_2Cl_2, reflux, 1.5 h, 72%; (i) Bu_4NBr_3 (0.01 equiv), $HOCH_2CH_2OH$ (5.4 equiv), $CH(OMe)_3$ (2 equiv), 1.3 h, 92%; (j) H_2, $Pd(OH)_2$ (0.3 equiv), MeOH–buffer (pH = 7) 3:1, 5 h, 88%.

Hydrogenation of **9** with 10% Pt/C provided compound **15** in 92% yield. To our delight, methanolysis of compound **15** proceeded faster than **9** to give 85% of the desired carboxylic acid **16** as the only regioisomer. We adopted Brown's one-pot procedure for converting an acid to an aldehyde.[9] The boroxine intermediate from borohydride reduction of acid **16** was directly oxidized without workup into aldehyde **17** with an overall 72% yield. Acetalization of aldehyde **17** with ethylene glycol generated compound **18** in 92% yield. Hydrogenation under buffered conditions provided alcohol **19**, which could be purified through crystallization. The improved sequence to generate compound **19** in Scheme 3b was superior in the number of steps, the overall yield and the ease of operation compared to the sequence shown in Scheme 3a.

Alcohol **19** was converted to iodide **4** in 99% yield (Scheme 4). Compound **4** was coupled with β-iodocyclopentenone (**3**) by applying Knochel's organozinc chemistry.[10] In practice, iodide **4** was converted to the alkylzinc iodide, which was then converted to the highly functionalized copper reagent by transmetallation with the soluble CuCN·2LiCl salt. This organocuprate intermediate was efficiently coupled to β-iodocyclopentenone (**3**) to form compound **20** in 82% yield.



Scheme 4. Reagents and conditions: (a) PPh_3 (1.2 equiv), I_2 (1.2 equiv), imidazole (1.2 equiv), Et_2O–CH_3CN = 3:1, 0 °C to rt, 1 h, 99%; (b) activated zinc, 40 °C, 4 h, CuCN·2LiCl, −10 °C, 10 min then β-iodocyclopentenone (**3**), 0 °C to rt, 2 h, 82%; (c) (i) Me_2CuLi, TMSCl, Et_3N, HMPA, 0 °C to rt, 77%; or MeMgBr (1.4 eq), CuBr·Me_2S (0.05 equiv), HMPA, TMSCl, 50%, (ii) $TiCl_4$ (2 equiv), 4 Å MS, CH_2Cl_2, 0 °C, 1 h, 54% from Me_2CuLi, 64% from MeMgBr; (d) TsOH·H_2O, benzene, 80 °C, 30 min, 73% from **21a**, 79% from **21b**.

Sequential conjugate addition/intramolecular Mukaiyama aldol reaction was applied to form the [5–7–6] tricyclic ring system of guanacastepene A. In the event, treatment of **20** with lithium dimethylcuprate in the presence of TMSCl resulted in the conjugate addition of a methyl group and in situ formation of the TMS enol ether. The intramolecular Mukaiyama aldol reaction of the TMS enol ether with the dioxolane acetal was mediated by titanium tetrachloride. Due to the robust nature of dioxolane,[11] it was necessary to carry out the Mukaiyama aldol reaction at a higher temperature than in the case of dimethyl acetal. Only two isomers, **21a** and **21b**, were formed in the cyclization, with some eliminated products **2** and **22**. Elimination of the C2 hydroxyethoxy group from **21a** and **21b** was facilitated by treatment with a catalytic amount of *p*-toluenesulfonic acid to furnish **2** and **22**, respectively. The ethoxy group at C5 survived the elimination conditions. The structures of compounds **2** and **22** were unequivocally established by X-ray crystallographic analysis (Fig. 1).[12] The ratio of the sum of the desired *trans*-dimethyl isomers **21a** and **2** to the sum of the *cis*-dimethyl isomers **21b** and **22** was 1:1 with conjugate addition of lithium dimethylcuprate. The ratio improved to 1.2:1 with methyl magnesium bromide addition catalyzed by copper bromide dimethyl sulfide complex.[13]

In summary, we have synthesized a highly functionalized [5–7–6] tricyclic framework **2** of guanacastepene A with C11 and C8 methyls and C5 oxygenation in 12 steps from (*trans*-ethoxyvinyl)tributyltin (**7**). The convergent synthesis of a highly functionalized intermediate **2** was possible through the intermolecular Diels–Alder reaction between 1,1,4-trisubstituted diene **5** and maleic anhydride, coupling of advanced six membered ring precursor **4** with β-iodocyclopentenone (**3**), and the sequential conjugate addition/intramolecular Mukaiyama aldol reaction. Future work will include improvement of the stereoselectivity of the C11 methyl introduction and completion of the total synthesis.

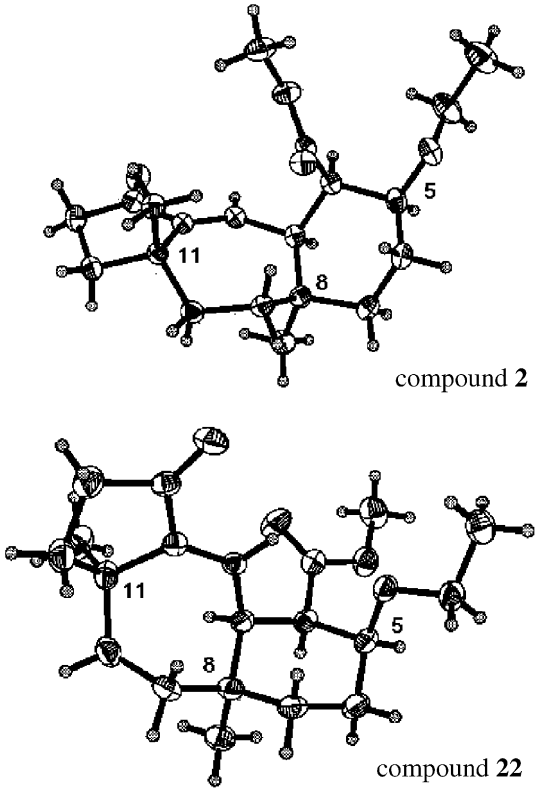


Figure 1. X-ray structures of compounds **2** and **22**.

Acknowledgements

We gratefully acknowledge UCLA (Seed Grant) and Amgen Inc. (Young Investigator's Award to O.K.) for financial support. H.V.C. acknowledges a USPHS national research service award (GM08496). We thank Dr. Saeed Khan for X-ray structure determination of **2** and **22**. NMR spectra were collected on an Avance 500 supported by the National Science Foundation under equipment grant # CHE-9974928.

Supplementary data

Experimental procedures and characterization data for compounds **9**–**22** (PDF). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.187.

References and notes

1. (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116; (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.
2. Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.

3. (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569; (b) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123; (c) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030; (d) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399; (e) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789; (f) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185; (g) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188; (h) Magnus, P.; Waring, M. J.; Olliver, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947; (i) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605; (j) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063; (k) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975; (l) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233; (m) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, 411; (n) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113; (o) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063; (p) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033; (q) Nguyen, T. M.; Seifert, R.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959; (r) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363; (s) Boyer, F.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469; (t) Boyer, F.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817; (u) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923; (v) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491; (w) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624; (x) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165; (y) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613.
4. Only two examples of the application of 1,1-dialkyl-4-alkoxy acyclic diene in Diels–Alder reaction were found: (a) Carballares, S.; Craig, D.; Lane, C. A. L.; MacKenzie, A. R.; Mitchell, W. P.; Wood, A. *Chem. Commun.* **2000**, 1767; (b) Kienzle, F.; Mergelsberg, I.; Stadlwieser, J.; Arnold, W. *Helv. Chim. Acta* **1985**, *68*, 1133.
5. (a) Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432; (b) Hibino, S. Personal communication.
6. Compound **8** was derived from 4-iodo-3-methyl-3-buten-1-ol through benzyl protection (NaH, BnBr, THF, quantitative). For preparation of 4-iodo-3-methyl-3-buten-1-ol, see: Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.
7. Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugina, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.
8. At −40 °C, two sets of peaks corresponding to two conformers of **13** were observed. At a higher temperature (75 °C), the peaks merged into one set with the right number of carbons and protons. The discovery of the conformational exchange phenomenon is very important as the compounds possessing the acetal functionality such as compounds **4**, **14**, and **18**–**20** generally behave the same with inadequate number of proton and carbon peaks in the NMR spectra taken at room temperature.
9. Brown, H. C.; Rao, C. G.; Kulkarni, S. U. *Synthesis* **1979**, 704.
10. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
11. (a) For literature examples of Mukaiyama aldol reactions employing dioxolane, see: Alexakis, A.; Chapdelaine, M. J.; Posner, G. H.; Runquist, A. W. *Tetrahedron Lett.* **1978**, *19*, 4205; (b) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.
12. Crystallographic data (excluding structure factors) for **2** and **22** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 249697 and 249698. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
13. Williams, D. R.; Heidebrecht, R. W. *J. Am. Chem. Soc.* **2003**, *125*, 1843. The yield of the enol ether formation is unoptimized.