HETEROCYCLES, Vol. 59, 2003, No. 1, pp. 81 - 85, Received, 12th July, 2002

STUDIES TOWARDS THE BIOMIMETIC SYNTHESIS OF GINSENOYNE L; EFFICIENT SYNTHESIS OF 2'-EPI-GINSENOYNE L

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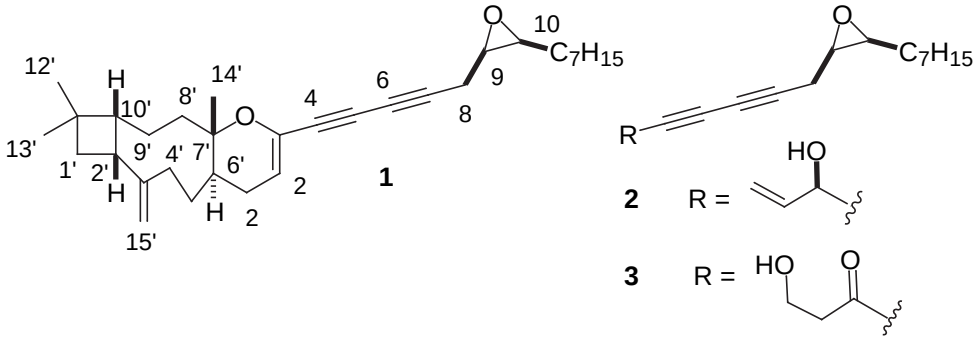
Abstract - The biomimetic synthesis of 2'-*epi*-gynsenyone L has been accomplished in 7 steps and in good yield through the novel use of bis-acetylenic enones as hetero Diels-Alder dienes for the mild and easy generation of dihydropyrans.

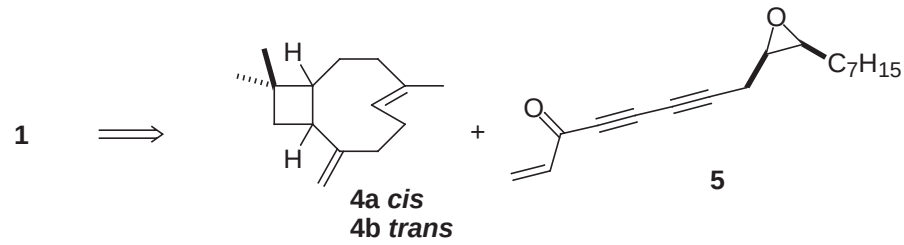
As part of our continuous efforts in the biomimetic synthesis of natural products,[1] we have become interested in the biomimetic synthesis of gynsenoyne L (**1**). Ginsenoyne L (**1**) was isolated in 2000 by Hirakura and coworkers in 6.8×10^{-5}% yield from the roots of *Panax ginseng*, and its structure proposed on the basis of 2-D NMR spectral analysis, and NMR spectral data comparison with panaxydol (**2**).[2] *Panax ginseng* is an important plant in traditional oriental medicine for the treatment of diabetes, as well as, psychiatric and neurological disorders.[3]



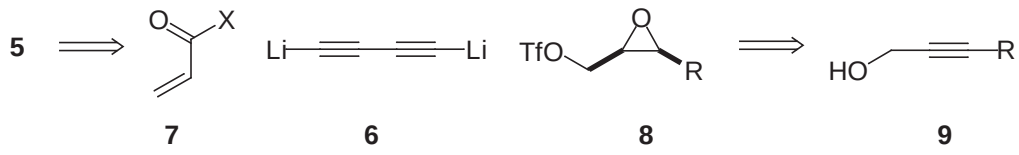
Although, no biological data has been reported for ginsenyone L (**1**), it's proposed structure shares a significant number of structural motifs both with panaxydol (**2**), and with PQ-7 (**3**), which are bis-acetylenic epoxides with powerful biological activity against leukaemia L1210 cell lines.[4,5] Structurally, ginsenyone L (**1**) contains the aforementioned bis-acetylenic epoxide unit as well as a dihydropyran unit attached to a sesquiterpene core. Unfortunately, there are still some uncertainties with respect to the complete structural determination of ginsenyone L (**1**), namely, the assumed unusual *cis* stereochemical make up of the $C_{2'}$-$C_{10'}$ ring junction, the stereochemistry of the epoxide side chain, and the absolute stereochemistry of ginsenyone L (**1**) as a whole.

In our biomimetic approach, we envisioned ginsenyone L (**1**) as having originated from the novel hetero

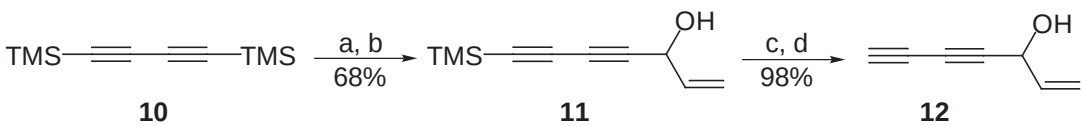
Diels-Alder reaction between rare 9-*epi*-β-caryophellene (**4a**), and the bis-acetylenic enone ginsenyone E (**5**). Although the use of enones as hetero Diels-Alder dienes has been previously demonstrated,[6] we are unaware of reports of the use of the potentially highly reactive bis-acetylenic enones under such conditions. We were also interested in comparing the uncommon *cis* $C_{2'}$-$C_{10'}$ ring junction reported for ginsenyone L (**1**) with that of abundantly occuring *trans*-β-caryophyllene (**4b**) which exhibits the thermodynamically more favorable junction at the bridgehead position.[7] Thus, we investigated the feasibility of a biomimetic hetero Diels-Alder reaction between the bis-acetylenic enone (**5**) and the trisubstituted *E*-double bond in β-caryophyllene (**4**), by initially modelling commercially available *trans*-β-caryophyllene (**4b**) as the heterodienophile. The regiochemical and stereochemical aspects of this hypothesis can be supported in FMO theory which would favour such regioselective and stereoselective addition to the more substituted double bond over the disubstituted exocyclic double bond.[8] Furthermore, there is evidence that *trans*-double bonds in medium sized rings are more reactive than expected based solely on steric strain.[9]



Enone (**5**) could be in turn synthesised from the stepwise bis-alkylation of a bis-acetylene dianion equivalent (**6**) with the acid derivative (**7**), and triflate (**8**)[10] which itself could be obtained from the corresponding alkynol (**9**) through reagent controlled Sharpless epoxidation chemistry.[11] Based upon the reported structures of panaxydol (**2**)[4] and PQ-7 (**3**),[5] we targeted the *2R, 3S* triflate (**8**).



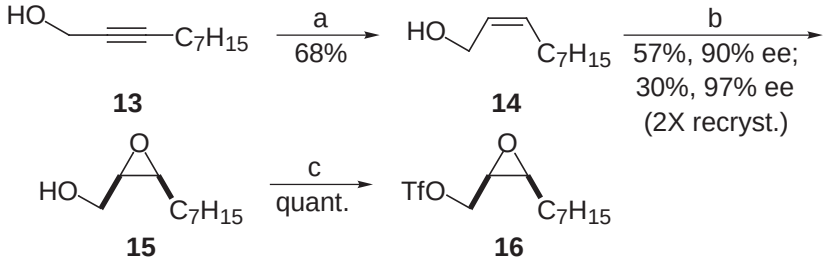
Our synthesis began with commercially available dialkyne (**10**), which was readily monodesilylated, and the resulting anion traped with acrolein to generate the desired alkenol (**11**) in good yield. Removal of the second trimethylsilyl unit from the newly formed diynol proceeded cleanly to afford the terminal dialkyne (**12**) in excellent yield.



Reagents and Conditions: a) MeLi - LiBr, THF, -20 ˚C, 3 h; b) Acrolein, -20 ˚C, 1 h; c) NaOH (1M, aq), Et_2O, 1 min 45 sec; d) HCl (2M, aq).

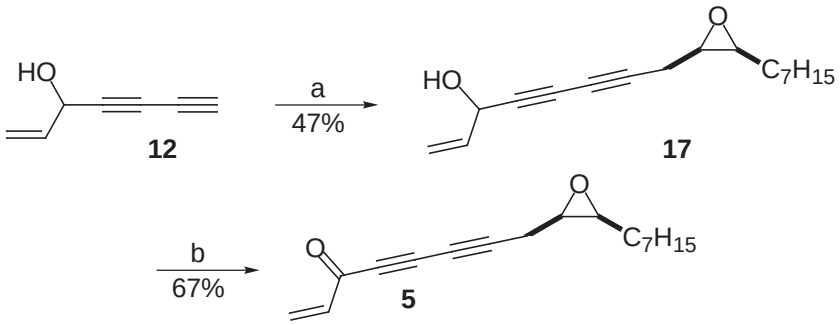
The synthesis of the epoxy-triflate fragment (**8**) began with commercially available alkynol (**13**), which was selectively reduced to the desired *Z*-alkenol (**14**) through Cram's method.[12] Reagent controlled

epoxidation of allylic alkenol (**14**) under Sharpless conditions[11] proceeded cleanly to afford the desired *cis*-epoxy-alcohol (**15**) in good yield and in excellent ee. The epoxy-alcohol (**15**) was then readily triflated[13] to generate the required crude epoxy-triflate (**16**).



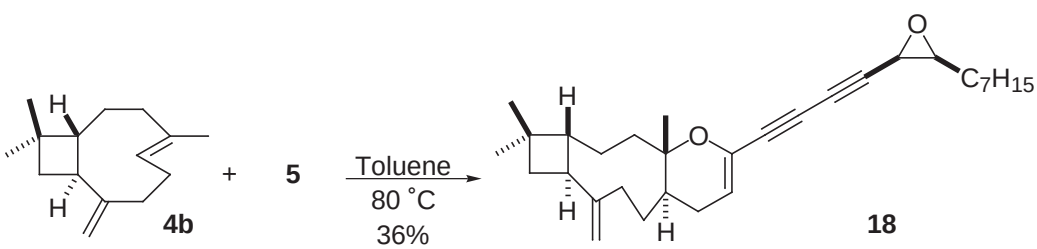
Reagents and Conditions: a) 5% Pd/$BaSO_4$, H_2, Quinoline, MeOH; b) D-(-)-DIPT, $Ti(OiPr)_4$, TBHP, DCM, -20 ˚C; c) Tf_2O, TEA, DCM, -78 ˚C.

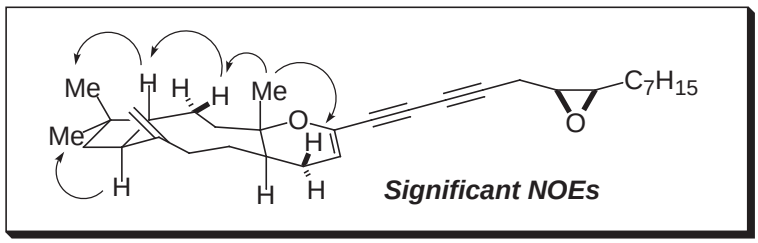
With the dialkyne unit (**12**), and the epoxy-triflate (**16**) at hand, the required alkyne alkylation for the introduction of ginsenyone L's side chain was then attempted. Thus treatment of dialkynol (**12**) with 2 equivalents of *n*-butyllithium followed by trapping with the crude triflate (**16**) proceeded cleanly to afford the desired coupled adduct (**17**) in reasonable yield. Oxidation of the remaining secondary alcohol in (**17**) was then cleanly performed under Bolm's conditions[14] to generate the pivotal enone (**5**) in good yield.



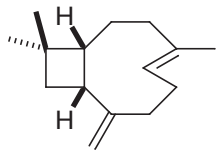
Reagents and Conditions: a) 2 eq. *n*-BuLi, THF:DMPU (6:1), -78 ˚C, 1 h; then **16**, -78 ˚C, 16 h; b) TEMPO (10 mol %), nBu_4Br (30 mol %), oxone (2 eq), toluene, 3.5 h.

Finally, the crucial hetero-Diels-Alder reaction of enone (**5**) with *trans*-β-caryophyllene (**4b**) was attempted under carefully monitored conditions. Thus, treatment of enone (**5**) with a five-fold molar excess of **4b** in toluene at 80 ˚C for five days afforded the desired dihydropyran unit (**18**) in good yield, as a major (>80%) *cis*-adduct with *endo* selectivity by 1-D, 2-D ^1H NMR spectrometry, and NOE analysis.[15] We were encouraged by these results, as they demonstrated the feasibility of our biomimetic approach without the use of either Lewis acid catalysts or extreme temperatures.

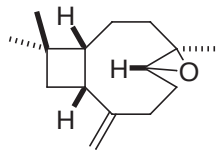




Furthermore, NMR spectral comparisons of this new ginsenyone analogue (**18**), with known β-caryophyllenes (**4b**, **20**), and 9-epi-β-caryophyllene derivatives (**4a**, **19**), would seem to corroborate the bizarre, yet apparently accurately reported $C_{2'}$-C_{10}, *cis* ring junction in ginsenyone L (**1**).



4a



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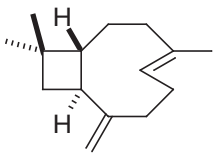
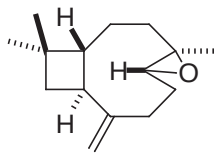


4b



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^{1}H NMR ($CDCl_3$, 500 MHz) chemical shifts for *gem*-dimethyl groups in β-caryophyllenes, 9-epi-β-caryophyllenes, gynsenyone L (**1**), and gynsenyone analogue (**18**).[7]			
β-caryophyllenes	δ (ppm)	9-epi-β-caryophyllenes	δ(ppm)
4b	0.97, 0.99	**4a**	0.90, 1.19
20	0.97, 0.99	**19**	0.90, 1.19
18	0.98, 1.02	**1**	0.90, 1.19

In conclusion, we have shown the versatility of bis-acetylenic enones as hetero Diels-Alder dienes for the mild and easy generation of dihydropyrans. We have also demonstrated the feasibility of our efficient biomimetic synthetic approach to the synthesis of ginsenyone L (**1**) by synthesising 2'-*epi*-gynsenyone L (**18**) in 7 steps and in reasonable overall yield. The hetero Diels-Alder reaction between ginsenyone E (**5**) and 9-*epi*-caryophyllene (**4a**) will be attempted as soon as a sample of 9-*epi*-caryophyllene (**4a**) can be procured.

REFERENCES.

1. J. E. Baldwin, A. V. M. Mayweg, K. Neumann, and G. J. Pritchard, *Org. Lett.*, 1999, **1,** 1933; J. E. Baldwin, R. M. Adlington, F. Roussi, P. G. Bulger, R. Marquez, and A. V. M. Mayweg, *Tetrahedron*, 2001, **57**, 7409.

2. K. Hirakura, K. Sugama, M. Morita, K. Nakajima, H. Sasaki, M. Okada, and H. Sato, *Heterocycles,* 2000, **53**, 2451.
3. K. Hirakura, M. Morita, K. Nakajima, Y. Ikeya, and H. Mitsuhashi, *Phytochemistry*, 1991, **30**, 3327.
4. K. Shim-Il, L. You-Hui, and A. Byung-Zun, *Arch. Pharm. Med. Chem.,* 1999, **332**, 133.
5. Y. Fujimoto, H. Wang, M. Satoh, and N. Takeuchi, *Phytochemistry*, 1994, **35**, 1255.
6. L. A. Telan, C. D. Poon, and S. A. Evans, *J. Org. Chem.*, 1996, **61**, 7455; A. B. Padias, S. T. Hedrick, and H. K. Hall, *J. Org. Chem.,* 1983, **48**, 3787.
7. S. F. R. Hinkley, N. B. Perry, and R. T. Weavers, *Phytochemistry,* 1994, **35**, 1489, and references therein.
8. R. M. Adlington, J. E. Baldwin, G. J. Pritchard, A. J. Williams, and D. J. Watkin, *Org. Lett.*, 1999, **1**, 1937, and references therein.
9. K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Natural Product Chemistry, Academic Press, New York, 1974, Vol. 1, p. 87.
10. C. B. Chung, S. K. Chang, and S. C. Shim, *Bull. Korean Chem. Soc.,* 1991, **12**, 122.
11. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.,* 1980, **102**, 5974; B. E. Rossitier, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237; R. A. Johnson and K. B. Sharpless, 'Comprehensive Organic Synthesis' Vol. 7, Asymmetric Epoxidations, Pergamon, Oxford, 1990, Chapter 3.2.
12. D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*,1956, **78**, 2518.
13. H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.,* 1990, **31**, 4609.
14. C. Bolm, A. S. Magnus, and J. P. Hildebrand, *Org. Lett.,* 2000, **2**, 1173.
15. The presence of other stereoisomeric forms of **18** (<10%) in the crude reaction product may result from the equilibrating conformers of **4b**, see: H. Shirahama, E. Osawa, B. R. Chabra, T. Shimokawa, T. Yokono, T. Kanaiwa, T. Amiya, and T. Matsumoto, *Tetrahedron Lett.,* 1981, **22**, 1527.