COMMUNICATION

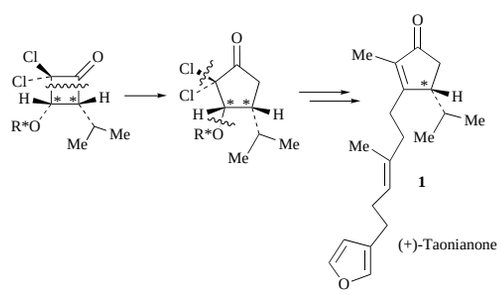
Convergent, enantioselective synthesis of the novel furanoditerpene (+)-taonianone through facially selective chiral olefin–ketene [2+2] cycloaddition

Alice Kanazawa, Philippe Delair, Mehrnaz Pourashraf and Andrew E. Greene*

Université Joseph Fourier, LEDSS, BP 53X, 38041 Grenoble Cedex, France

(+)-Taonianone, an unusual diterpene from the brown alga *Taonia australasica*, has been enantioselectively prepared through [2+2] cycloaddition of chloromethylketene with a chiral enol ether.

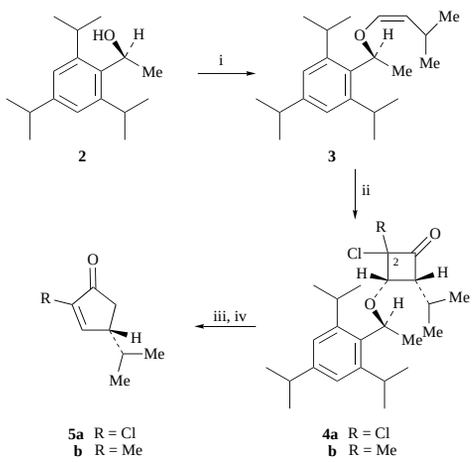
It has previously been shown that diastereofacially selective cycloaddition of dichloroketene with chiral olefins can be effectively used to prepare γ-lactam-derived, γ-lactone and cyclopentanone natural products.[1] A salient feature of this methodology is that α,β unsaturation can be introduced through reductive elimination under conditions mild enough to preclude epimerization at sensitive chiral centers,[2] and thus the approach seemed particularly well suited for a synthesis of (+)-taonianone **1**.



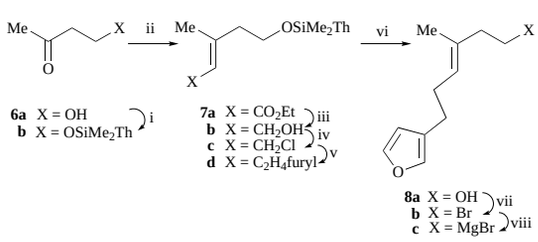
(+)-Taonianone, a furanoditerpene metabolite of the brown seaweed *Taonia australasica*, was isolated and structurally elucidated by Murphy *et al*. in 1981 and found to represent a new class of monocarbocyclic diterpenes.[3] Twice synthesized in natural form from (*R*)-(−)-carvone, it has thus been shown to possess the absolute stereochemistry that is indicated in structure **1**.[4] In this communication, an efficient asymmetric synthesis of this natural product is described, based on what we believe to be the first example of chirality control through facial selectivity in an alkylchloroketene–chiral enol ether [2+2] cycloaddition.

Our initial convergent approach to (+)-taonianone began with the conversion of readily available[5] (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol **2** into its (*Z*)-isopent-1-enyl ether **3** (67% yield) (Scheme 1). Cycloaddition of this chiral olefin with dichloroketene[6] proceeded with excellent facial selectivity (95:5) to give dichlorocyclobutanone **4a**, which in the presence of diazomethane underwent smooth, regioselective ring enlargement[7] to provide the corresponding dichlorocyclopentanone. This derivative on exposure to chromous perchlorate[2] in aqueous acetone produced highly enantioenriched α-chlorocyclopentenone **5a** (53% overall or 81% per step from **3**).

Of the several side chain preparations examined, that shown in Scheme 2 was found to be the most practical and reproducible. The homoallylic bromide **8b** so obtained was converted into the Grignard reagent **8c**, which under cuprous iodide catalysis added conjugately to enone **5a** [eqn. (1)]. The resulting α-chloroenolate on treatment with methyl iodide in HMPA



Scheme 1 *Reagents and conditions:* i, isopentenyl methyl ether, NBS, CH_2Cl_2; then Zn–Cu, NH_4Cl, MeOH; then separation of *E* and *Z* isomers, equilibration of the *E* isomer [$Hg(OAc)_2$], 67%; ii, Cl_3CCOCl (series **a**) or $MeCl_2CCOCl$ (series **b**), Zn–Cu, diethyl ether; iii, CH_2N_2, Et_2O, MeOH; iv, $Cr(ClO_4)_2$, acetone; then MeCOCl, proton sponge, CH_2Cl_2, 53% (series **a**), 43% (series **b**) (3 steps)

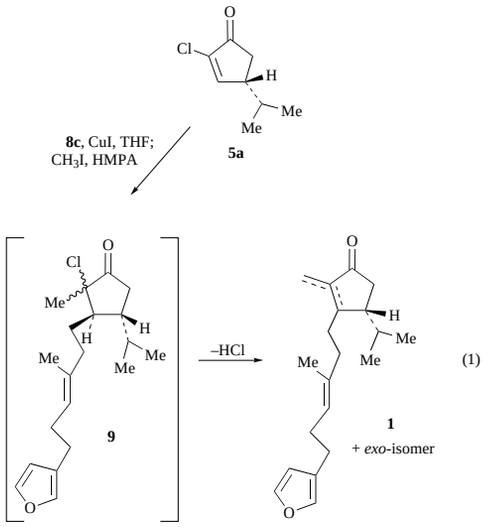


Scheme 2 *Reagents and conditions:* i, $Me_2ThSiCl$, DMAP, CH_2Cl_2, 92%; ii, triethyl phosponoacetate, LDA, THF 55%; iii, DIBAL-H, CH_2Cl_2; iv, MsCl, LiCl, 2,4,6-trimethylpyridine, DMF, 82% (2 steps); v, 3-(chloromethyl)furan, Mg, THF; then **7c**, Li_2CuCl_4, THF; vi, HF, CH_3CN, 69% (2 steps); vii, CBr_4, Ph_3P, Et_2O, 93%, viii, Mg, THF [Th = thexyl (1,1,2-trimethylpropyl)]

underwent methylation to give cyclopentanone **9**, which *in situ* slowly lost HCl[8] to provide directly (+)-taonianone, but unfortunately in very low overall yield. Since the yield, in part, was compromised by the occurrence of a substantial amount of exocyclic elimination, a consequence of poor stereoselectivity in the enolate methylation, an alternative approach designed to obviate the need for stereocontrol was examined.

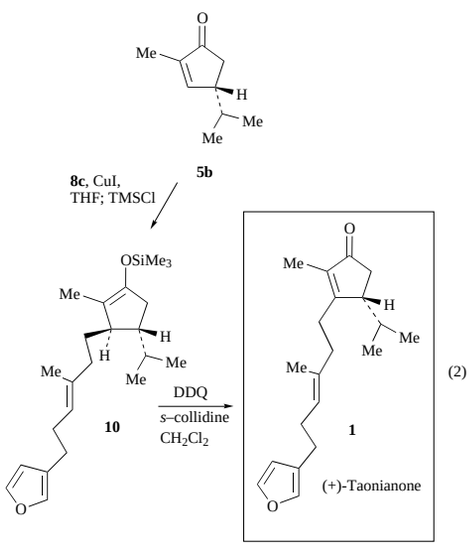
Chloromethylketene[6] also was found to react with enol ether **3** with a high degree of facial selectivity (94:6) to produce the expected cyclobutanone **4b** as the major product (3:1 epimeric mixture at C-2) (Scheme 1).† Diazomethane-promoted ring expansion of **4b** proceeded cleanly, albeit more slowly than with

† Diastereomeric upgrading of this 94:6 mixture through recrystallization led to unacceptable loss of material.



4a, to give the corresponding cyclopentanone, which on reductive elimination provided the α-methylcyclopentenone **5b** in 43% overall yield (75% per step).

Copper-catalyzed conjugate addition of the side chain Grignard reagent [eqn. (2)] followed by trapping of the resultant



enolate with trimethylsilyl chloride gave the desired enol ether **10**, which was found to undergo dehydrosilylation best with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of 2,4,6-trimethylpyridine (*s*-collidine)[9] in dichloromethane at 20 °C to provide **1** in 31% yield (56% per step). Synthetically derived (+)-taonianone‡ furnished spectroscopic data (IR, mass, ^{1}H NMR, ^{13}C NMR) in perfect accord with the literature values for the natural product.

Methods for creating carbon–carbon bonds with facial selectivity are of paramount importance in synthetic chemistry. This first asymmetric synthesis of (+)-taonianone [seven steps from (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol, 9% overall yield] demonstrates the potential of alkylchloroketene–chiral enol ether [2+2] cycloaddition for this purpose.

Experimental

J Values are given in Hz. $[a]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Taonianone 1

To a suspension of CuI (10 mg, 0.05 mmol) in dry THF (0.6 cm^3) at −50 °C was added 1 cm^3 of Grignard reagent **8c** (from 240 mg of bromide **8b**,§ 70 mg of Mg and 1.2 cm^3 of THF). The resulting mixture was warmed to −25 °C and then recooled to −90 °C and treated dropwise with a solution of enone **5b**¶ (30 mg, 0.22 mmol) in THF (0.5 cm^3). After being warmed to −55 °C and recooled to −78 °C, the mixture was treated with 0.54 cm^3 of a 1:1:1 mixture of TMSCl, hexane and triethylamine. The resulting reaction mixture was allowed to warm over 1 h to 20 °C and was poured into diethyl ether and saturated aqueous NH_4Cl, and the crude enol ether **10** was then isolated in the usual fashion.

A solution of the crude enol ether in dry dichloromethane (1 cm^3) containing 2,4,6-trimethylpyridine (92 mg, 0.76 mmol) was cooled to −10 °C and treated with a solution of DDQ (100 mg, 0.44 mmol) in 4 cm^3 of dry dichloromethane. After being allowed to warm over 20 min to 20 °C, the dark red solution was processed with diethyl ether in the usual way to afford the crude enone, which was purified on silica gel with 10% ethyl acetate in hexane as the eluent to provide taonianone **1** (20 mg, 31%); $[a]_D^{20}$ +10.3 (*c* 0.9, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2958, 2927, 2870, 1698 and 1641; δ_H 0.55 (3 H, d, *J* 6.9), 0.97 (3 H, d, *J* 6.9), 1.61 (3 H, s), 1.66 (3 H, s), 1.9–2.6 (11 H, m), 2.79 (1 H, br s), 5.17 (1 H, t, *J* 6.3), 6.22 (1 H, br s), 7.17 (1 H, br s) and 7.31 (1 H, br s); δ_C 8.0, 14.8, 15.9, 21.8, 24.8, 27.4, 27.6, 28.3, 34.7, 36.9, 45.8, 110.9, 124.7, 124.8, 134.5, 137.1, 138.8, 142.6, 175.5 and 209.5 (Found: M$^+$, 300.2097. $C_{20}H_{28}O_2$ requires *M*, 300.2089).

Acknowledgements

We thank Professor J. Lhomme for his interest in our work. Financial support from the CNRS (UMR 5616) and the Université Joseph Fourier are gratefully acknowledged.

References

1 A. E. Greene, F. Charbonnier, M. J. Luche and A. Moyano, *J. Am. Chem. Soc.*, 1987, **109**, 4752; M. B. M. de Azevedo, M. M. Murta and A. E. Greene, *J. Org. Chem.*, 1992, **57**, 4567; M. M. Murta, M. B. M. de Azevedo and A. E. Greene, *ibid*., 1993, **58**, 7537; M. B. M. de Azevedo and A. E. Greene, *ibid*., 1995, **60**, 4940; P. Nebois and A. E. Greene, *ibid*., 1996, **61**, 5210.
2 A. E. Greene and F. Charbonnier, *Tetrahedron Lett*., 1985, **26**, 5525.
3 P. T. Murphy, G. March and R. J. Wells, *Tetrahedron Lett*., 1981, **22**, 1555.
4 F. Kido, T. Abe and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun*., 1986, 590; M. Huckestein, W. Kreiser and V. Rüschenbaum, *Helv. Chim. Acta*, 1987, **70**, 445.
5 P. Delair, A. M. Kanazawa and M. B. M. de Azevedo, *Tetrahedron: Asymmetry*, 1996, **7**, 2707.
6 For a review on ketene cycloaddition chemistry, see: J. A. Hyatt and P. W. Raynolds, *Org. React*., 1994, **45**, 159.
7 A. E. Greene and J. P. Deprés, *J. Am. Chem. Soc.*, 1979, **101**, 4003.
8 J. P. Deprés and A. E. Greene, *J. Org. Chem*., 1980, **45**, 2036.
9 T. L. Fevig, R. L. Elliott and D. P. Cunan, *J. Am. Chem. Soc.*, 1988, **110**, 5064.

Paper 7/01629H
Received 7*th March* 1997
Accepted 8*th May* 1997

‡ The synthetic material displayed the expected 94:6 enantiomeric ratio (HPLC, Chiracel OD-H, 5 μm, hexane–propan-2-ol, 98:2, 0.5 cm^3 min^{-1}).

§ Bromide **8b**: ν_{max}(neat)/cm^{-1} 2969, 2925, 2856, 1670, 1565, 1503, 1449, 1164, 1029 and 876; δ_H 1.59 (3 H, s), 2.23 (2 H, m), 2.48 (4 H, m), 3.41 (2 H, t, *J* 7.4), 5.25 (1 H, br t, *J* 6.9), 6.26 (1 H, s), 7.20 (1 H, m) and 7.32 (1 H, m); δ_C 15.6, 24.7, 28.4, 31.6, 42.8, 111.0, 124.7, 127.1, 132.6, 138.9 and 142.6; *m*/*z*: 244 and 242 (M$^+$), 163, 135, 81, 53 and 41 (Found: C, 54.46; H, 6.55%; M$^+$, 242.0308. Calc. for $C_{11}H_{15}OBr$: C, 54.34; H, 6.25%; *M*, 242.0306).

¶ Enone **5b**: $[a]_D^{20}$ −119 (*c* 3.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2960, 2911, 2880, 1707, 1644, 1454, 1339 and 1072; δ_H 0.86 (3 H, d, *J* 6.7), 0.90 (3 H, d, *J* 6.7), 1.66 (1 H, m), 1.72 (3 H, m), 2.04 (1 H, A of ABX, *J* 2.1, 18.9), 2.40 (1 H, B of ABX, *J* 6.3, 18.7), 2.6 (1 H, m) and 7.24 (1 H, m); δ_C 10.0, 19.8, 19.9, 31.7, 38.7, 45.4, 141.8, 160.8 and 209.8 (Found: M$^+$, 138.1049. $C_9H_{14}O$ requires *M*, 138.1045).