Jeudi 8 novembre 2007 - Exercice - Christophe

Enantioselective total synthesis of (+)-guanacastepene N

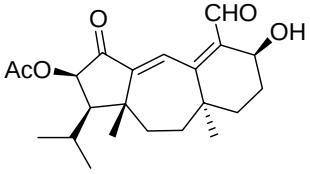
Shin Limura, Larry E. Overman, Ralph Paulini, Armen Zakarian *J. Am. Chem. Soc.* **2006**, *128*, 13095-13101.

The guanacastepenes were isolated in 2000 from an endophytic fungus growing on the tree *Daphnosis Americana* in Costa Rica (Guanacaste Conservation Area).[1]

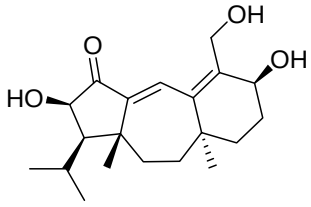
Guanacastepenes present antibacterial activity against :

- Methicillin-resistant *Staphylococcus aureus*,
- Vancomycin-resistant *Enterococcus faecium*,

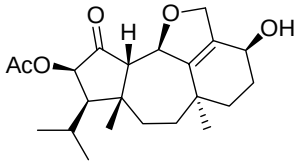
but these structures are able to lyse human blood cells…



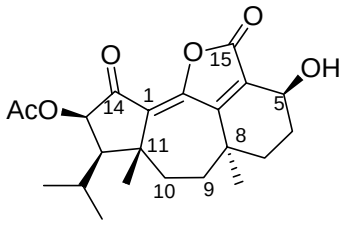
(+/-)-guanacastepene A[2]
Danishefsky **2002**



(+/-)-guanacastepene C[3]
Mehta **2005**



(+)- and (-)-guanacastepene C[4]
Shipe and Sorensen **2006**



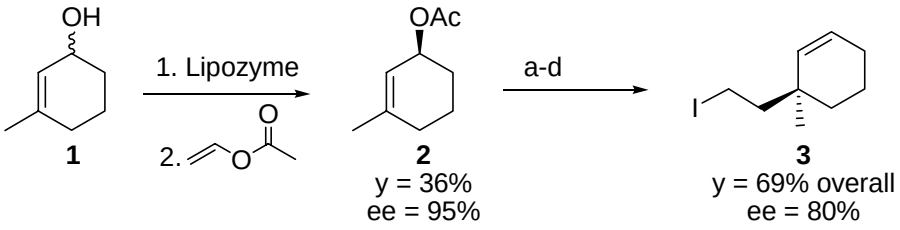
(+)-guanacastepene N
Limura **2006**

Three challenges for total synthesis:

- Five stereocenters among which two quaternary carbons C_8 and C_{11},
- All-cis relationship of the three adjacent substituents on the five-membered ring,
- Central seven-membered ring.

[1] (a) S. F. Brady, M. P. Singh, J. E. Janso, J. Clardy, *J. Am. Chem. Soc*. **2000**, *122*, 2116-2117. (b) S. F. Brady, S. M. Bondi, J. Clardy, *J. Am. Chem. Soc*. **2001**, *123*, 9900-9901.
[2] D. S. Tan, G. B. Dudley, S. J. Danishefsky, *Angew. Chem. Int. Ed*. **2002**, *41*, 2185-2188 and 2188-2191.
[3] G. Mehta, K. Pallavi, J. D. Umarye, *Chem. Commun*. **2005**, 4456-4458.
[4] W. D. Shipe, E. J. Sorensen, *J. Am. Chem. Soc*. **2006**, *128*, 7025-7035.

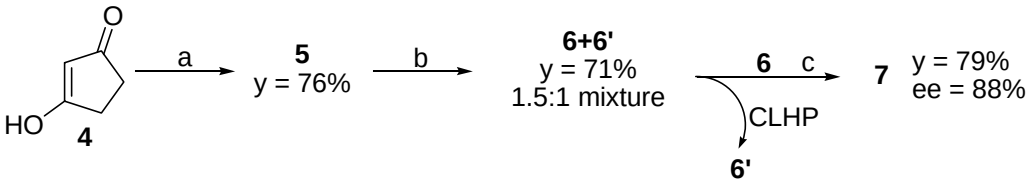
Synthesis of (*S*)-3-(2-iodoethyl)-3-methylcyclohex-1-ene **3**.



(a) LDA, THF, -78 °C, 30 min, then DMPU, TBSCl, -78 °C → rt, 30 min; (b) toluene, 80 °C, 10 h; (c) DIBAL-H, toluene, -78 °C → rt, 1 h; (d) I_2, Ph_3P, imidazole, CH_2Cl_2, 0 °C → rt, 5 h.

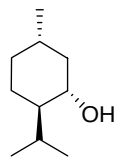
LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TBSCl = *tert*-butyldimethylsilyl chloride; DIBAL-H = diisobutylaluminium hydride; rt = room temperature.

Synthesis of (*R*)-4-isopropyl-3-methylcyclopent-2-enone **7**.

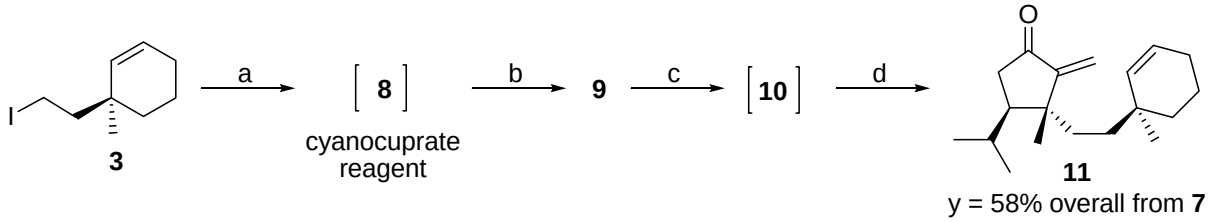


(a) (+)-menthol, *p*-TsOH, benzene, 80 °C, 9 h; (b) LDA, THF, -78 °C, 20 min, then Et_2Zn, 2-iodopropane, DMPU, -78 °C → rt, 20 h; (c) MeLi, THF, -78 °C → 0 °C, 3 h, aqueous $NaHSO_4$.

(+)-menthol :

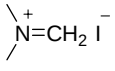


Coupling of building blocks **3** and **7**.

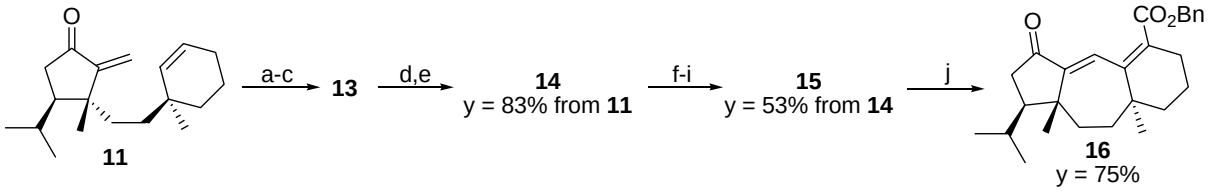


(a) *t*-BuLi (1 equiv.), Et_2O-pentane, -78 °C, 30 min, then CuCN (1 equiv.), -78 °C → -30 °C, then (b) Me_3SiBr (1 equiv.), THF, and add **7** (0.7 equiv.), -78 °C, 6 h; (c) formaldiminium iodide **12**, 2,6-lutidine, DMF, 0 °C, 1 h, then (d) MeI, Et_2O, rt, 12 h, and K_2CO_3, CH_2Cl_2/MeOH,H_2O (4:1:3), rt, 3 h.

formaldiminium iodide **12** :



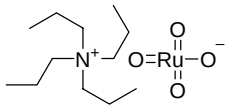
Formation of guanacastepene scaffold.



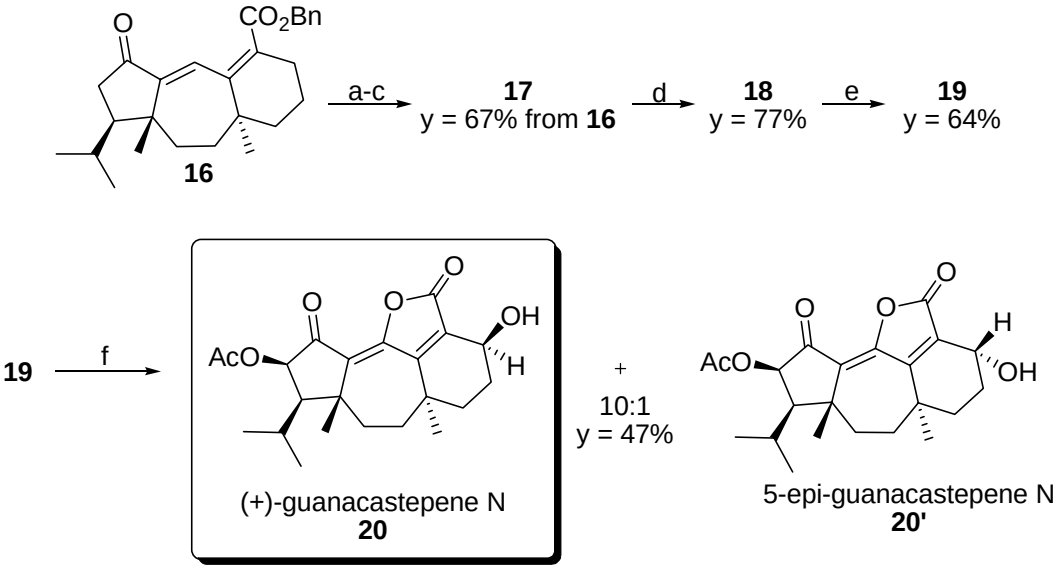
(a) *m*-CPBA, CH_2Cl_2, 0 °C, 3 h; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -78 °C, 1 h; (c) TBSCl, imidazole, CH_2Cl_2, rt, 30 min; (d) $LiEt_3BH$, THF, 0 °C, 2 h; (e) NMO, TPAP, CH_2Cl_2, rt, 1 h; (f) $LiN(SiMe_3)_2$, THF, -78 °C → -30 °C, 10 min, then DMPU, benzyl cyanoformate, -78 °C → -45 °C, 10 min; (g) $KN(SiMe_3)_2$, THF, -78 °C, 20 min, then Tf_2O, -78 °C, 10 min; (h) HF, $CH_3CN/MeOH/H_2O$ (8:2:1), 0 °C, 3 h; (i) NMO, TPAP, CH_2Cl_2, rt, 4 h;

(j) $Pd_2(dba)_3{\cdot}CHCl_3$ (12 mol %), dppb (24 mol %), KOAc, DMA, 80 °C, 12 h. **KEY STEP**

DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; NMO = *N*-methylmorpholine-*N*-oxide;
TPAP = tetra-*N*-propylammonium perruthenate :



Completion of the total synthesis of guanacastepene N **20**.



(a) TESOTf, Et_3N, CH_2Cl_2, -78 °C, 4 h; (b) DMDO, CH_2Cl_2/acetone, -78 °C, 10 h (dr = 9:1); (c) Ac_2O, Et_3N, DMAP, rt, 3 h; (d) Et_3SiH, $Pd(OAc)_2$, Et_3N, CH_2Cl_2, rt, 2 h; (e) NBS, benzoyl peroxide, CCl_4, reflux, 1.5 h (dr = 20 :1); (f) Bu_3SnH, air, toluene, rt, 16 h, then Ph_3P, $CHCl_3$, rt, 2 h.

TESOTf = triethylsilyltriflate; DMDO = dimethyldioxirane, DMAP = 4-*N*,*N*-(dimethylamino)pyridine; NBS = *N*-bromosuccinimide.

Longest route to (+)-guanacastepene N : 25 steps, **global yield = 0.008%** = 82% per step.