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Stereoselective synthesis of the bicyclo[5.3.0]decane portion of the diterpene antibiotic guanacastepene using a pyrylium-ylide [5+2] cycloaddition reaction

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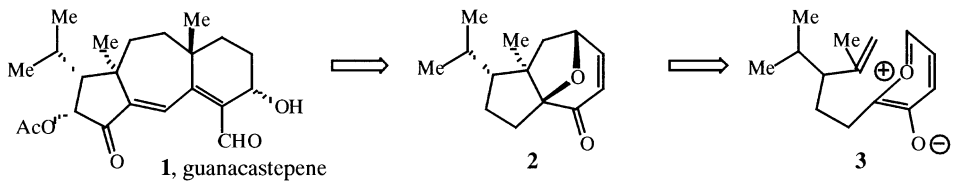
Abstract—Treatment of **14** with Ac_2O/Et_3N resulted in [5+2] cyclization to give **2**, which was further elaborated into **20**, thus establishing the required stereochemistry in the top-half of guanacastepene **1**.

In 2000 Clardy et al. reported the X-ray structural determination of the fungal-derived diterpene antibiotic guanacastepene **1** (Scheme 1).[1] The compound was isolated from an extract of a fungus from the branch of a *Daphnopsis americana* tree. The extract showed antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*. Methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecalis*. The major active component of the extract was **1**. The absolute configuration of **1** is currently not established.[7]

Recently, Snider has reported the synthesis of the hydroazulene portion of **1** using a $EtAlCl_2$-initiated cyclization of a γ,δ-unsaturated ketone.[2] In this letter we describe the stereoselective construction of the bicyclo[5.3.0]decane (hydroazulene) portion of **1** with the correct *trans*-1,4-angular methyl group stereochemistry using a pyrylium-ylide cyclization.[3] The strategy outlined in Scheme 1 is based on the premise that the [5+2] cyclization of the pyrylium-ylide **3** will result in **2**, which has the angular methyl group in an axial conformation and the isopropyl group is equatorial.

The first requirement of the strategy depicted in Scheme 1 was a convenient synthesis of the aldehyde **9** (Scheme 2). Treatment of isobutylmethyl ketone with pyrrolidine/*p*-TsOH (removal of water) gave the enamines **4** and **5** (1:5), which were exposed to acrylonitrile to give **7** as the major adduct after fractional distillation.[4] Small amounts of the isomeric adduct **6** were present. Wittig methenylation of **7** with Ph_3PCH_3Br/NaH/DMSO converted **7** into **8** in quantitative yield. Finally, diisobutylaluminum hydride reduction of **8** gave **9** (83%). While this sequence of reactions provided gram quantities of **9**, the route does not lend itself particularly readily to the synthesis of **9** in an enantioselective form.

We have examined a different strategy for the synthesis of **8**, and hence **9**, that is amenable to making accessible both enantiomers of **8**. Treatment of 2-methyl-2-cyclopenten-1-one with isopropylmagnesium chloride in the presence of cuprous iodide (cat.), followed by alkylation of the enolate with methyl iodide gave **10** (74%) (Scheme 3). While methods are available that accom-



Scheme 1.

Keywords: guanacastepene; antibiotic; pyrylium-ylide; conjugate addition.

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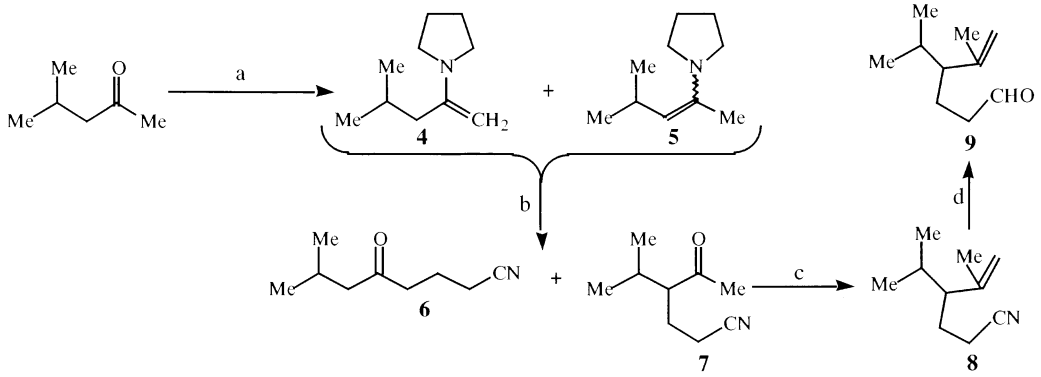
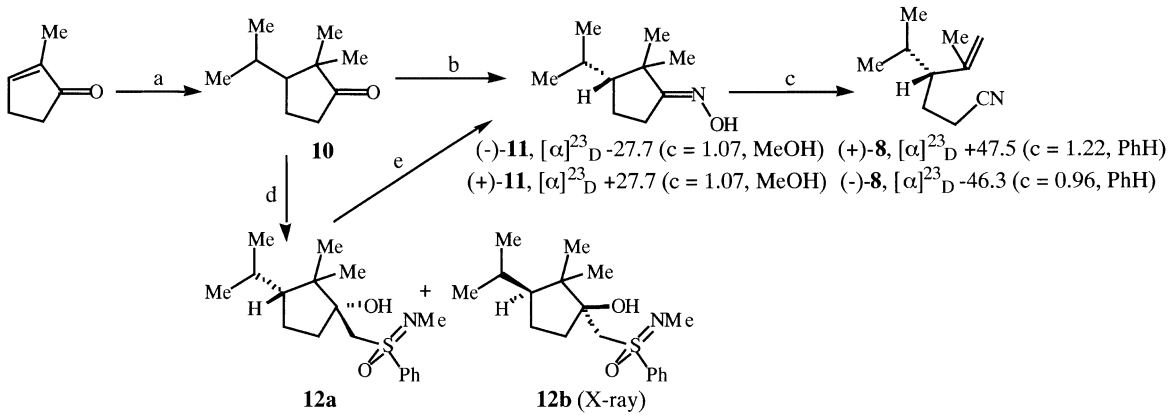


Scheme 2. *Reagents and conditions*: (a) pyrrolidine (1.2 equiv.)/*p*-TsOH (cat.)/PhH reflux 24 h, **4** and **5** (1:5) by ^{1}H NMR; (b) acrylonitrile (1.0 equiv.)/6 h/25°C **7** (58% over two steps); (c) Ph_3PCH_3Br (1.1 equiv.)/NaH/DMSO/25°C, add **7** (1 h), **8** (100%); (d) DIBAL-H (1.2 equiv.)/CH_2Cl_2/−78°C/2 h, **9** (83%).



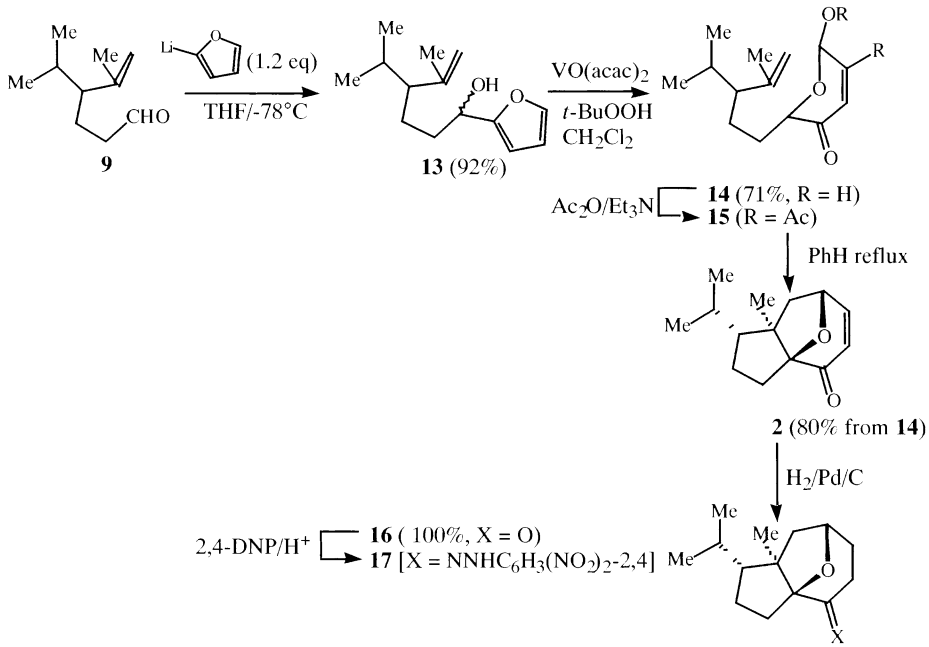
Scheme 3. *Reagents and conditions*: (a) (i) *i*-PrMgCl (1.1 equiv.)/CuI (0.15 equiv.)/THF, −30 to −5°C (ketone added over 45 min at −30°C, and warmed to −5°C over 30 min); (ii) MeI (5 equiv.)/−5 to 23°C/12 h, **10** (74%); (b) $NH_2OH{\cdot}HCl$ (1.2 equiv.)/pyridine (5 equiv.)/EtOH/23°C/12 h, **11** (96%); (c) PCl_5 (1.1 equiv.)/2,6-lutidine (2 equiv.)/Et_2O/23°C, oxime added over 5 min and stirred for 10 min, **8** (77%) and 11% of amide by-products; (d) (+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (1.15 equiv.)/*n*-BuLi (1.1 equiv.)/THF/−78°C/6 h, **12a** and **12b** (88%, 1:1, and traces of one other stereoisomer <5%); (e) (i) *n*-PrOH reflux/12 h; (ii) $NH_2OH{\cdot}HCl$ (1.5 equiv.)/pyridine (10 equiv.)/12 h, **11** (86%).

plish conjugate addition reactions with good enantioselectivity, their application to this specific situation did not look particularly optimistic. Therefore, it was decided to examine the Johnson sulfoximine ketone resolution methodology since this would allow access to both enantiomers of **8**.[5]

Treatment of **10** with lithio (+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine in THF at −78°C gave the separable adducts **12a** (45%) and **12b** (43%) in excellent yield along with traces (<5%) of another stereoisomer. The structure and absolute stereochemistry of **12b** was established by X-ray crystallography. Heating the separated adducts **12a** and **12b** in 1-propanol at reflux liberated the ketone **10**, which was converted in situ by addition of $NH_2OH{\cdot}HCl$/pyridine to give the crystalline oximes (−)-**11** (as shown) and (+)-**11** (mirror image), respectively. Beckman fragmentation[6] of (−)-**11** was accomplished by treatment with PCl_5/2,6-lutidine/Et_2O to give (+)-**8** (77%). This route provides a relatively straightforward way to prepare enantiomerically enriched (+)-**8** and its mirror image (−)-**8**.[7]

Addition of 2-lithiofuran to **9** gave **13**, which was oxidatively rearranged by treatment with *tert*-butyl hydroperoxide/vanadyl acetoacetate/CH_2Cl_2 to give **14** (71%) (Scheme 4). Acetylation of **14** gave **15**, which on heating in benzene at reflux cyclized to give **2** (80%) along with a small amount of another stereoisomer (95:5 by ^{1}H NMR). The structure and relative stereochemistry of **2** were ascertained by hydrogenation to give **16**, and conversion of **16** into the crystalline 2,4-dinitrophenylhydrazone **17**. The structure of **17** was determined by X-ray crystallography, and Fig. 1 shows an ORTEP representation. It can be clearly seen that the isopropyl and the adjacent angular methyl group are *cis* to one another in the correct configuration as required for **1**.

The enone **2** requires the introduction of an appropriate β-substituent that will eventually comprise part of the six-membered ring of **1**, and also allow stereoselective conjugate addition of the angular methyl group (Scheme 5). Following our previous protocols[8] **2** was treated with $Br_2/CH_2Cl_2/Et_3N$ resulting in **18**. Exposure



Scheme 4.

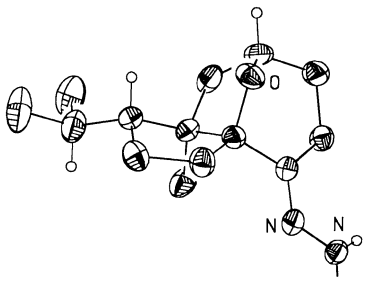
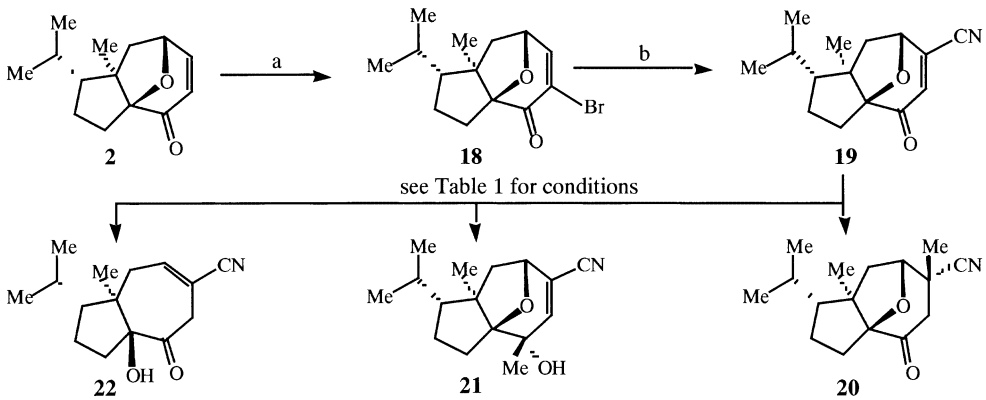


Figure 1. View of **17** with labeled heteroatoms. Thermal ellipsoids are scaled to 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale. The 2,4-$(NO)_2C_6H_3$-group has been removed for clarity.

of **18** to KCN/Et_3N/*n*-Bu_4NI (cat.) resulted in addition–elimination to give the β-cyanoenone **19** in excellent yield. Methyl lithium containing lithium bromide reacted with **19** to give the required adduct **20** (1,4) along with the expected 1,2-adduct **21** in a ratio of 1:2. The structure and stereochemistry of **20** was proven by X-ray crystallography (Fig. 2). Table 1 lists a variety of reaction conditions that were tried to improve the ratio in favor of **20**. Standard dimethylcopper lithium addition (entry 6) resulted in **20** and the reduction product **22** (X-ray). It was found that the required adduct **20** became the major product (88%) when **19** was treated with Me_3Al in the presence of $Ni(acac)_2$ (cat.) at 0°C (entries 12–14).[9]

The pyrylium-ylide cyclization to give **2**, and subsequent elaboration into **20**, provides a solution to the construction of the bicyclo[5.3.0]decane with control over relative and absolute stereochemistry in the top portion of **1**.[10]



Scheme 5. *Reagents and conditions*: (a) (i) Br_2/CH_2Cl_2; (ii) Et_3N, **18** (86%); (b) (i) KCN (7 equiv.)/*n*-Bu_4NI (cat.); (ii) Et_3N (14 equiv.), **19** (82%).

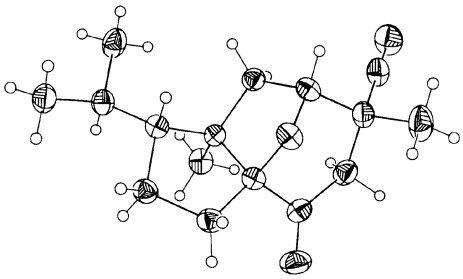


Figure 2. View of **20** with labeled heteroatoms. Thermal ellipsoids are scaled to 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale.

Table 1. Reactions of **19** with various Me transfer reagents (product ratios of **20**:**21**:**22**)

Conditions		**20**	**21**	**22**
1. MeLi/LiBr (1.2 equiv.)/THF −78°C		1	2	0
2. MeLi/MAD/hexane 25°C		1	14	0
3. MeMgCl (5 equiv.)/CuI (5 equiv.)/THF 0°C	1	0	1	
4. MeMgCl (10 equiv.)/CuI (5 equiv.)/THF 0°C	0	0	1	
5. Me_2CuLi (3.0)/hexane −10°C		1	7	1
6. Me_2CuLi (5.0)/THF 0°C	1	0	3	
7. Me_2Zn/Ni(acac)$_2$(cat.)/LiBr/THF 25°C		1	1	0
8. Me_2Zn/Ni(acac)$_2$(1 equiv.)/LiBr/THF 25°C	1	2	0	
9. Me_2Zn (10 equiv.)/Ni(acac)$_2$ (10%)/THF 25°C[a]	0	1	2	
10. Me_2Zn/LiBr/THF/25°C	2	1	0	
11. Me_3Al/THF 25°C		1	20	0
12. Me_3Al (2 equiv.)/Ni(acac)$_2$ (10%)/THF 25°C[b]		8 (80%)	1	0
13. Me_3Al (1.5 equiv.)/Ni(acac)$_2$ (10%)/THF 25°C		8 (82%)	1	0
14. Me_3Al (1.5 equiv.)/Ni(acac)$_2$ (10%)/THF 0°C		20 (88%)	1	0

[a] Me_2Zn added over 2 h.
[b] Me_3Al added over 30 min.

Acknowledgements

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7. While the absolute configuration of guanacastepene was not reported in the original paper (Ref. 1) it appears that it is most likely as shown for **1**, and therefore corresponds to (+)-**8** (Dr. Jon Clardy is thanked for this information).
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10. Spectral data ^{1}H NMR data for key compounds: Compound **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.65–7.53 (m, 3H), 5.91 (br s, 1H), 3.38–3.26 (m, 2H), 2.71 (s, 3H), 1.84–1.33 (m, 5H), 1.10 (q, J=9.0 Hz, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.89 (d, J=6.6 Hz, 3H), 0.80 (d, J=6.6 Hz, 3H). Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (d, J=0.9 Hz, 1H), 4.76 (d, J=1.5 Hz, 1H), 2.37–2.25 (m, 2H), 2.19–2.07 (m, 1H), 1.99–1.87 (m, 1H), 1.82–1.73 (m, 1H), 1.68–1.44 (m, 1H), 1.59 (s, 3H), 0.93 (d, J=6.6 Hz, 3H), 0.84 (d, J=6.6 Hz, 3H). Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.81 (d, J=1.5 Hz, 1H), 4.65 (d, J=1.5 Hz, 1H), 2.38–2.22 (m, 2H), 2.00–1.86 (m, 1H), 1.68–1.20 (m, 3H), 1.61 (s, 3H), 0.94 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.6 Hz, 3H). Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, J=9.6, 4.5 Hz, 1H), 5.97 (d, J=9.6 Hz, 1H), 4.85 (dd, J=7.2, 4.5 Hz, 1H), 2.78–2.62 (m, 1H), 2.36 (dd, J=12.0, 7.2 Hz, 1H), 2.20–2.03 (m, 1H), 1.76–1.45 (m, 5H), 0.93 (d, J=6.3 Hz, 3H), 0.91 (d, J=6.3 Hz, 3H), 0.84 (s, 3H). Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (dd, J=6.0, 1.8 Hz, 1H), 2.77–2.41 (m, 4H), 2.08–1.97 (m, 2H), 1.84–1.73 (m, 1H), 1.65–1.35 (m, 3H), 1.59 (s, 3H), 0.98 (d, J=6.3 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H), 0.89 (s, 3H).