Pergamon

Tetrahedron Letters 42 (2001) 7311–7313

TETRAHEDRON LETTERS

A stereoselective synthesis of naturally occurring (+)-20*R*-dihydrocleavamine by photo-[2+2]-cycloreversion

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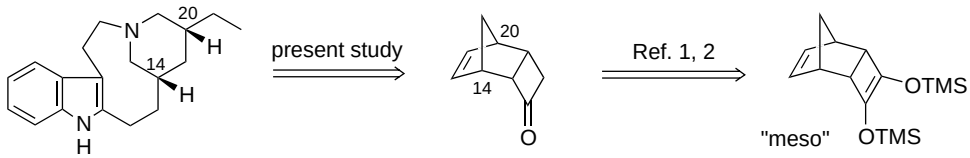
Received 8 August 2001; revised 21 August 2001; accepted 23 August 2001

Abstract—A stereoselective synthesis of (+)-20*R*-dihydrocleavamine, an alkaloid from *Pandaca eusepala* and *Tabernamontana eglandulose*, has been developed using an enantiopure tricyclic ketone accessible from a *meso* precursor by employing a photo-[2+2]-cycloreversion reaction as the key step.

We have developed an efficient method for the preparation of an enantiopure tricyclic ketone **2**[1,2] containing a four-membered ring starting from the readily accessible *meso* ene-1,2-diol bis-trimethylsilyl ether **3**.[3] Since it has been previously reported[4] that racemic **2** collapsed on irradiation to give *cis*-4-vinylcyclopent-2-enylketene by a photo-induced [2+2]-cycloreversion of the four-membered ring, we were attracted to the conversion of the enantiopure ketone (−)-**2** into (+)-20*R*-dihydrocleavamine **1**, an *Iboga* indole alkaloid isolated from *Pandaca eusepala*[5] and *Tabernaemontana eglandulose*,[6] by employing the photo-cleavage reaction as the key step[7] (Scheme 1).

The synthesis was commenced with a modification of the cyclopentene double bond of the ketone (−)-**2** to alleviate its discrimination from the side-chain double bond generated after the irradiation. Thus, dihydroxylation of (−)-**2** was first carried out to give selectively 1,2-diol **4**, $[\alpha]_D^{29}$ −180.7 (*c* 1.0, $CHCl_3$), as a single isomer probably having *exo*-configuration in 93% yield under catalytic osmylation conditions. On irradiation[4] in methanol in a Pyrex tube, **4** furnished methyl ester **6**, $[\alpha]_D^{27}$ −39.8 (*c* 1.7, $CHCl_3$), in one-step in 57% yield, indicating that the expected photo-[2+2]-cycloreversion reaction did occur to give rise to vinyl-ketene **5**, which was reacted spontaneously with the solvent under the conditions. Catalytic hydrogenation of **6** was next carried out to yield **7**, $[\alpha]_D^{27}$ −25.2 (*c* 1.0, $CHCl_3$), carrying the 20*R*-ethyl functionality of the target molecule **1**. On sequential periodate cleavage and borohydride reduction in the same flask, **7** afforded γ-lactone **9**, $[\alpha]_D^{26}$ −0.5 (*c* 1.0, $CHCl_3$), via diol **8** through a concurrent cyclization during workup. The primary hydroxy functionality remaining in **9** was then replaced by an azide functionality to give the primary azide **11**, $[\alpha]_D^{27}$ +0.7 (*c* 1.5, $CHCl_3$), via mesylate **10**. Overall yield of **11** from (−)-**2** was 43% in six steps (Scheme 2).

Catalytic hydrogenation of the azide **11** in methanol containing ammonia[8] brought about spontaneous lactamization to give the seven-membered lactam **12**, $[\alpha]_D^{27}$ +1.6 (*c* 0.7, $CHCl_3$), which was sequentially *O*-benzylated and *N*-*tert*-butoxycarbonylated (Boc)[9] to give imide **14**, $[\alpha]_D^{26}$ −24.4 (*c* 0.6, $CHCl_3$), via the secondary amide **13**, $[\alpha]_D^{26}$ −13.1 (*c* 1.0, $CHCl_3$). Reduction of **14** with lithium triethylborohydride[9] at low temperature, followed by treating the crude product with methanolic



(+)-20*R*-dihydrocleavamine **1** (−)-**2** **3**

Scheme 1.

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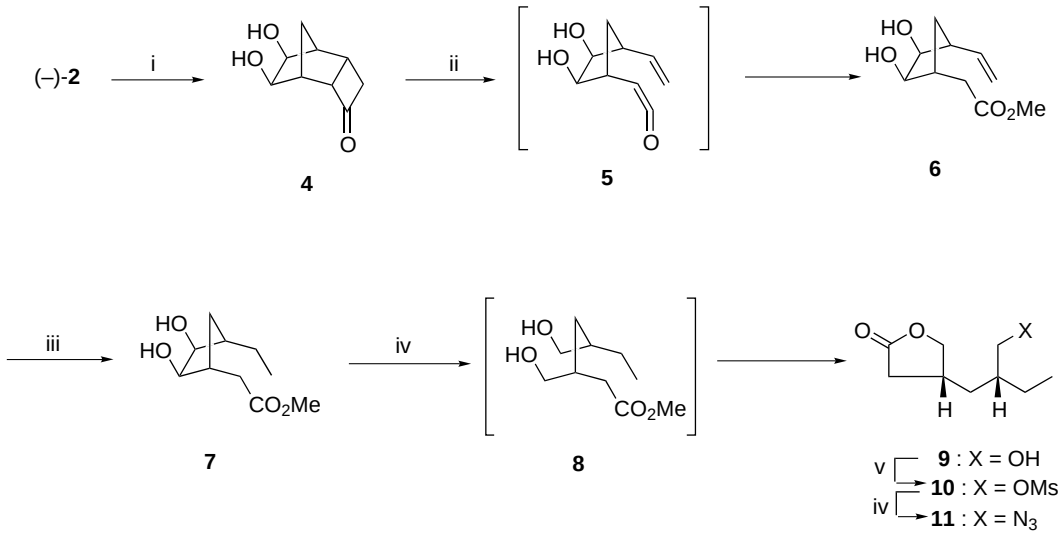
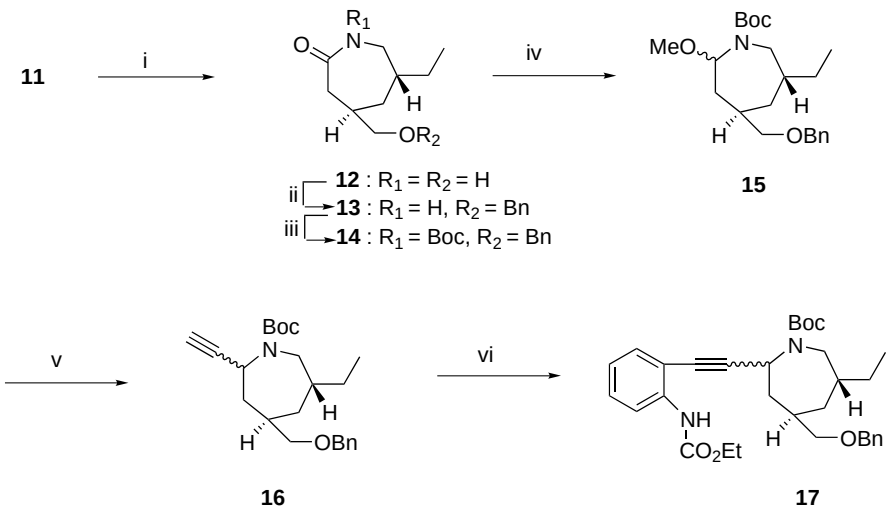


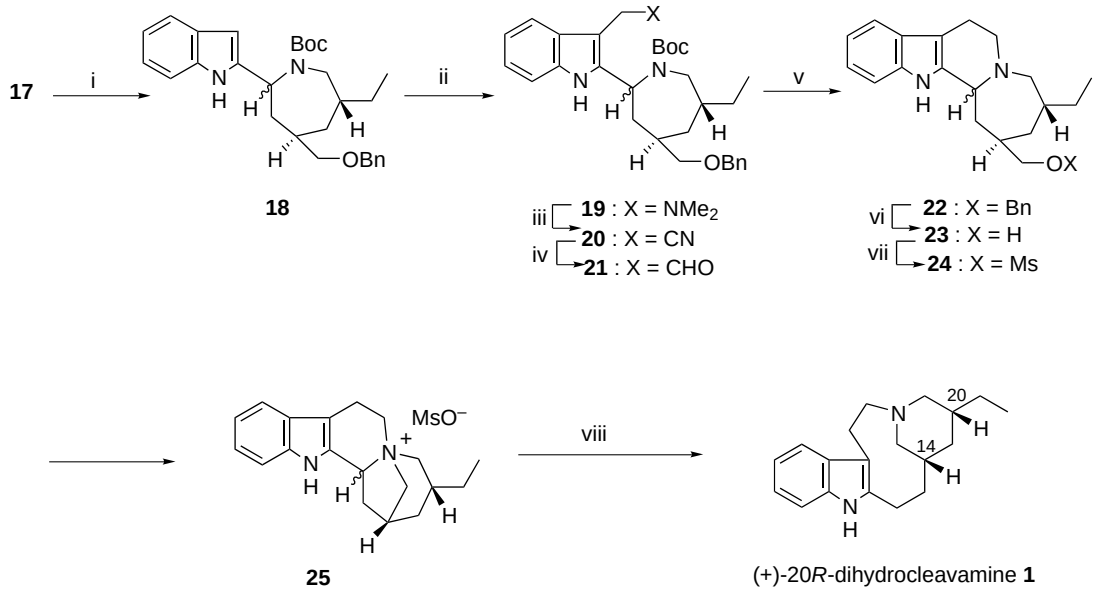
Scheme 2. *Reagents and conditions*: (i) OsO_4 (cat.), 4-methylmorphorine *N*-oxide (NMO) (93%). (ii) *hv*, MeOH (57%). (iii) H_2, PtO_2, AcOEt (99%). (iv) $NaIO_4$, then $NaBH_4$ (83%). (v) Ms–Cl, Et_3N. (vi) NaN_3, DMF, 80°C (92%, two steps).

hydrogen chloride, yielded the *N*-Boc-amino acetal **15** as an epimeric mixture. Treatment of **15** with the acetylide generated in situ from trimethylsilylacetylene with butyllithium in dichloromethane in the presence of dimethylaluminum chloride[10] allowed the replacement of the methoxy functionality by trimethylsilylacetylene to furnish the seven-membered amine carbamate **16** after desilylation of the resulting silylacetylene mixture with tetrabutylammonium fluoride (TBAF). The Sonogashira reaction[11] of **16** with *N*-ethoxycarbonyl-2-iodoaniline proceeded without difficulty to afford the arylacetylene **17** as an epimeric mixture in excellent yield. Overall yield of **17** from **11** was 47% in six steps (Scheme 3).

We have so far synthesized some indolic natural products by employing the indole synthesis[12] through 2-alkynylaniline precursors originally developed by Yamanaka and co-workers.[13] Employing the same conditions, **17** was refluxed with sodium ethoxide in ethanol to generate a two-substituted indole. The expected cyclization reaction took place to give the indole **18** in 65% yield as an epimeric mixture with spontaneous *N*-decarboethoxylation under the conditions. Employing standard procedure, the 3-acetaldehyde moiety was next installed on the indole ring of **18** obtained. Thus, on exposure to dimethylmethyleneammonium chloride,[14] **18** gave the gramine **19** which, after transformation into trimethylammonium iodide, was reacted with potassium cyanide to give 3-acetonitrile **20**. Reaction of **20** with diisobutylaluminum hydride[15] (DIBAL) at −78°C, followed by acid hydrolytic workup led to the generation of 3-acetaldehyde **21** in 75% overall yield through an imine intermediate.



Scheme 3. *Reagents and conditions*: (i) H_2, Pd–C, MeOH–NH_3 (95%). (ii) BnBr, NaH, THF (84%). (iii) $(Boc)_2O$, Bu^{t}Li, −78°C (100%). (iv) $LiEt_3BH$, −78°C, then HCl–MeOH (78%). (v) BuLi, TMS–acetylene, Me_2AlCl, CH_2Cl_2, −78 to 0°C, then TBAF (75%). (vi) Ar–I, $(Ph_3P)_2PdCl_2$ (cat.), CuI (cat.), Et_3N, reflux (89%).



Scheme 4. *Reagents and conditions*: (i) NaOEt, EtOH, reflux (65%). (ii) CH_2NMe_2Cl. (iii) MeI, then KCN, DMF, 100°C (83%, three steps). (iv) DIBAL, −78°C then 1.6N H_2SO_4 (92%). (v) BF_3, AcOH, CH_2Cl_2, 0°C then $NaBH_3CN$ (60%). (vi) Na, liq. NH_3, Bu^{t}OH, THF (85%). (vii) Ms–Cl, Et_3N. (viii) Na, liq. NH_3, Bu^{t}OH, THF (64%, two steps).

Upon treatment with boron trifluoride–acetic acid complex in dichloromethane, followed by sodium cyanoborohydride in the same flask, **21** furnished tetracyclic amine **22** in 60% yield through a sequential *N*-deprotection and reductive cyclization.[16] In order to construct the ring system of the target molecule **1**, **22** was debenzylated to give the primary alcohol **23** which was then mesylated to form ammonium salt **25**, directly, without isolation of the mesylate **24**. As has been established,[7a,17] both of the two epimers consisted of the mesylate **24** formed ammonium salt **25** as a mixture of epimers, which, on Birch reduction with sodium in liquid ammonia, allowed regioselective C–N bond cleavage to afford the targeted (+)-20*R*-dihydrocleavamine **1**, $[\alpha]_D^{26}$ +65.1 (*c* 0.2, $CHCl_3$) {natural: $[\alpha]_D$ +68 ($CHCl_3$);[5] $[\alpha]_D^{20}$ +133 (*c* 0.078, $CHCl_3$)[6]}, in 64% yield as a single product (Scheme 4).

In conclusion, we have developed an alternative route to (+)-20*R*-dihydrocleavamine from a readily accessible enantiopure precursor containing a cyclobutane moiety by employing a photo-[2+2]-cycloreversion reaction as the key step.

Acknowledgements

We are grateful to the Japan Society for the Promotion of Science for a scholarship (to R.M.K).

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