Pergamon

Tetrahedron Letters 43 (2002) 545–548

TETRAHEDRON LETTERS

The synthesis of a key intermediate en route to gelsemine: a program based on intramolecular displacement of the carbon–oxygen bond of a strategic oxetane

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Received 5 November 2001

Abstract—The synthesis of key intermediate **30** en route to gelsemine has been accomplished from known aldehyde **10** via oxetane **19** featuring stereospecific Claisen rearrangement and Lewis acid-catalyzed oxetane ring opening. © 2002 Published by Elsevier Science Ltd.

The appearance of the alkaloid gelsemine (**1**) (isolated from *Gelseminium semperverans*) in the chemical literature goes back to 1870.[1] Its structure was arrived at in 1959 through spectroscopic as well as degradative arguments advanced by Conroy,[2a] independent of a crystallographic determination conducted concurrently by Lovell and colleagues.[2b] The keen interest which gelsemine (**1**) has attracted from the point of view of total synthesis seems incongruous with the rather sketchy and anecdotal suggestions of its potential usefulness.[3] Clearly, it is the novel architecture of gelsemine, which has provoked many interesting strategies regarding possible routes for its assembly.[4]

Any proposal to reach gelsemine (**1**) must take note of the spiroanilide arising from the quaternary center at C7 (see Scheme 1). Further disconnection of the C7→N2 and O4→C3 bonds leads back to structure type **7** (see **7**→**8**→**1**). Progression from **7**→**8** requires suprafacial chirality transfer of a carboxyl equivalent with allylic transposition from C14→C7. The underside (α face) of **7** is quite hindered and prospects for introduction of a hydroxymethyl group at C16 by late stage joining of a C16–C17 bond were not inviting. Our approach to solving this problem called for an intramolecular displacement of a properly configured oxetane (see sequences **6**→**7**). *In this way the required C17 hydroxymethyl group is released as the pyrrolidine ring is established.* It was assumed that overall β hydroxylation with allylic transposition (en route from **6**→**7**) could be achieved.

The oxetane moiety in **6** would be fashioned from a C5–C16 olefinic linkage by an overall addition of a 'formaldehyde' residue in the proper regiochemical and stereochemical sense at the stage of **4**. The logic used for adding this formaldehyde element to the C5–C16 olefin in **5** was destined to be the key element of the program (vide infra). It was further proposed that the nucleophilic arm of the projected oxetane displacement reaction (see **6**→**7**) would have been derived from Curtius degradation of a suitable two carbon carboxylic acid, mounted at C20 (see structure **6**).

We conjectured about the possibility of concurrent presentation of the C20 vinyl group and the acetic acid residues in **6** via some form of a [3,3] rearrangement. The face selectivity issues in such a transformation would be a question for exploration. Assuming this matter could be resolved favorably, the prospect of reaching the allylic alcohol moiety of **5** from a C20 ketone virtually presented itself (see **4**→**5**).

Finally, in the retrosynthetic sense, it was hypothesized that **4** could have been derived from a divinyl cyclopropane→cycloheptadiene rearrangement (**3**→**4**). Compound type **3** might be reached by chain extension (cf. *o*-nitrobenzylidenation) of the aldehyde linkage of substrate type **2**. Depending on the precise nature of the structure, **2** could be a known compound (vide infra). In this and the accompanying paper, the synthesis of

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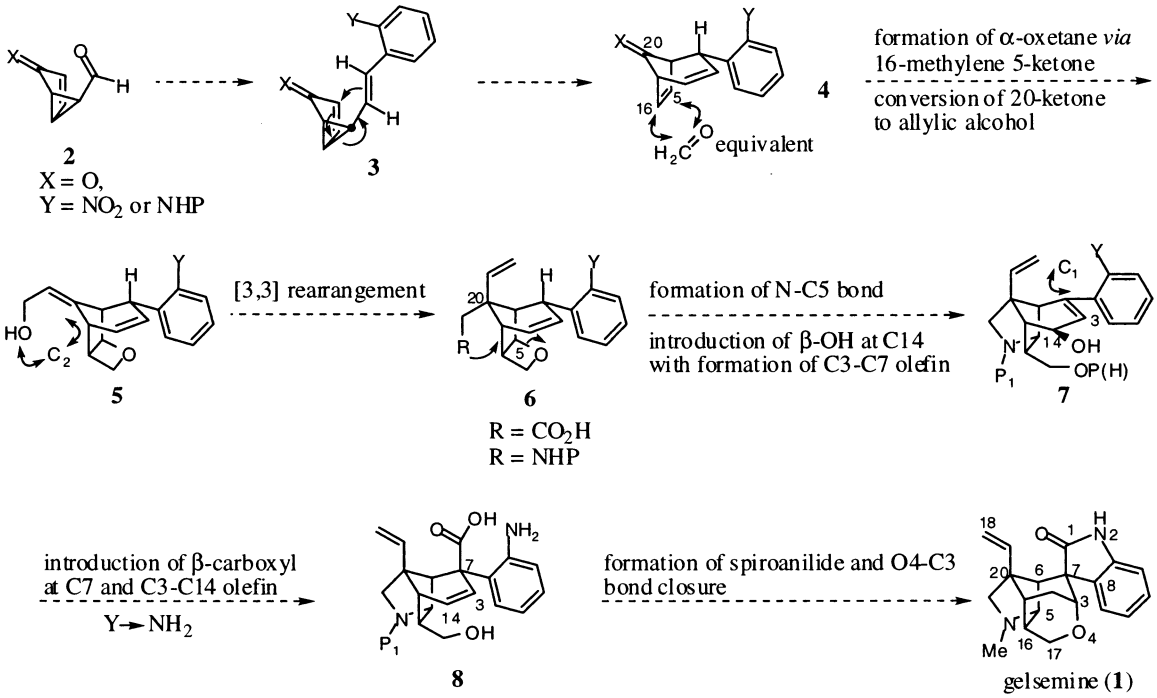
PII: S0040-4039(01)02212-2

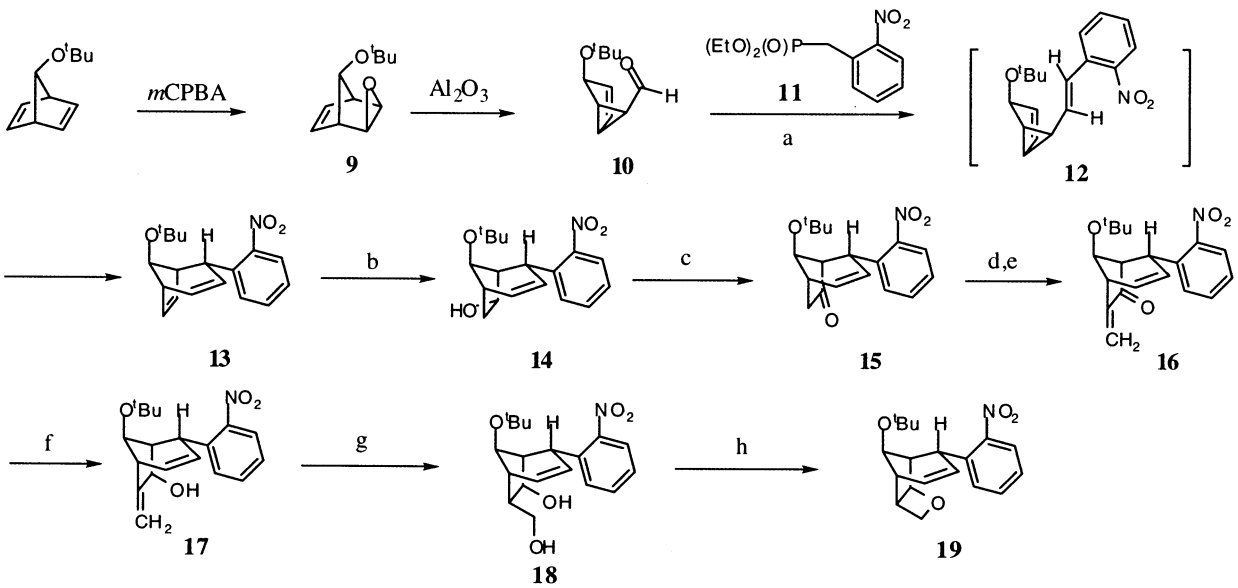


Scheme 1. Synthetic plan.

(±)-gelsemine (**1**) is described. While the proposal presented above was realized in broad terms, reduction to practice involved exposure to many interesting issues in organic synthesis.

The synthesis commenced with the epoxidation of 7-*t*-butoxynorbornadiene (Scheme 2).[5] Alumina promoted rearrangement of epoxide **9** afforded the known aldehyde **10**.[6] *o*-Nitrobenzylidenation[7] of this aldehyde, using phosphonate **11**, led to **13** presumably via divinylcyclopropane **12**. It was envisioned that ketone **15** would be an attractive type of intermediate to construct the critical oxetane moiety (cf. **5**).

In principle, **15** could be readily obtained from alcohol **14**, which might be reached by hydroboration–oxida-



Scheme 2. Synthesis of the oxetane ring. *Reagents and conditions*: (a) **11**, NaOMe, DMF, 0°C, 74%; (b) BH_2Cl·DMS, Et_2O, 0°C; $NaOH/H_2O_2$, 77%, +7% regioisomer;[8] (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 98.7%; (d) LiHMDS, TESCl, Et_3N, THF, −78 to 0°C; Eschenmoser's salt, CH_2Cl_2, 91%; (e) MeI, CH_2Cl_2/Et_2O; Al_2O_3, CH_2Cl_2, 95%; (f) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 99%; (g) 9-BBN dimer, THF; $NaOH/H_2O_2$, 88%; (h) MsCl, Et_3N, CH_2Cl_2, −78°C; NaHMDS, THF, −78°C, 91%. DMS = dimethyl sulfide; HMDS = hexamethyldisilazane; TESCl = chlorotriethylsilane; Eschenmoser's salt = $(CH_3)_2N{=}CH_2I$; 9-BBN = 9-borabicyclo[3.3.1]-nonane.

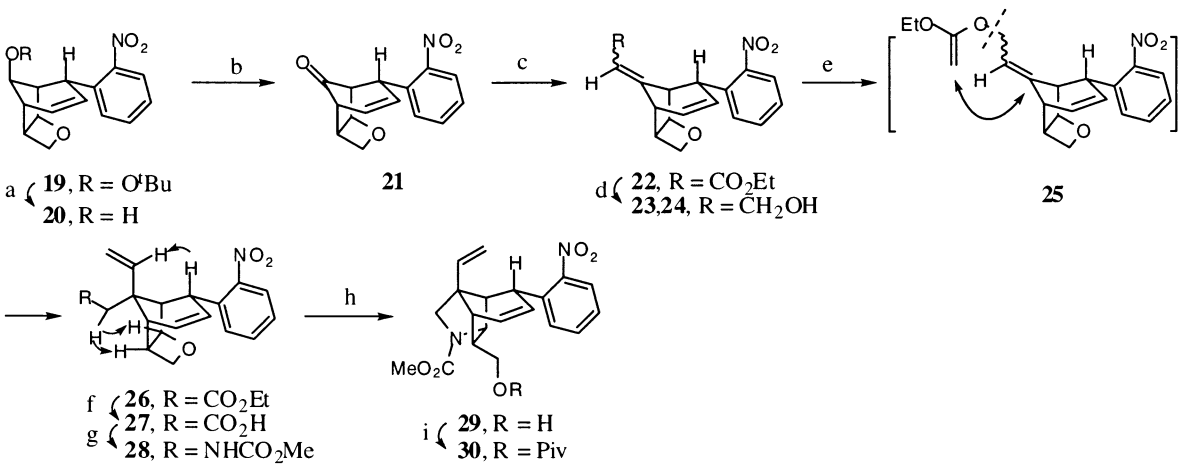
tion of **13**. Such a hydroboration reaction raised significant questions of chemoselectivity among the two double bonds, regioselectivity at the C5–C16 olefin and face selectivity. The key issue was that of regiopreference, even assuming, as we did, that reaction would be directed to the more strained and more exposed cyclopentene (C5–C16) linkage. Our findings and conjectures on this kind of hydroboration as well as related reactions, in a model closely related to **13**, have been discussed elsewhere.[8] In the event, treatment of **13** with BH_2Cl·DMS followed by oxidative workup, as shown, afforded a 11:1 ratio of alcohol **14** with the newly introduced alcohol at C5, relative to its isomer where the alcohol is at C16. Oxidation[9] of **14** afforded ketone **15**.

The campaign to install the oxetane commenced with dimethylaminomethylation of the silyl enol ether derived from **15**.[10] Following quaternization of the nitrogen, and base induced elimination, the α-methyleneketone **16** was in hand. *At this stage we could take advantage of β-face addition to both sp^2 centers (C5 and C16).* Hydride delivery at C5, in the context of a Luche reaction,[11] afforded **17**. Hydroboration of **17** also occurred from the β-face generating diol **18**.[12] From this diol intermediate, the α-face oxetane (**19**) was fashioned in a straightforward way as shown.

With the critical oxetane in hand, we entered the next phase of the projected plan hoping to reach a functional version of allylic alcohol **5**. We were anticipating a [3,3]-type rearrangement en route to structure type **6**. Following the cleavage of *t*-butyl ether **19**,[13] the resulting alcohol function in **20** was oxidized to afford ketone **21** (Scheme 3). Emmons-type condensation[14] was successful in terms of overall yield, but led to a 3:2 mixture of β,β-disubstituted steroisomers **22**. Each compound was converted by reduction to its allylic alcohol counterpart (**23** and **24**, respectively).[15] These isomers were individually treated with triethylorthoacetate as shown.[16] Remarkably, each allylic alcohol gave rise to a single and identical γ,δ-unsaturated ester **26** (presumably via **25**) with the β-vinyl and α-carboxymethyl functions at C20 in the required sense.[17] This stereochemical convergence might arise from the tendency of the enolate like component of the Claisen rearrangement step to glide over the five-membered ring fused to oxetane (see **25**→**26**). Additional cases must be evaluated to distinguish between possible steric or electronic factors in directing the face of the migration step.

Regardless of the reasons for this convergence, it provided smooth access to a key intermediate, **26**. Alkaline hydrolysis of the ethyl ester function served to release the free acid **27**.[18] Subjection of the latter to Curtius degradation, as practiced by Shiori, afforded urethane **28**.[19] As anticipated, the hitherto robust oxetane linkage, which had survived in the sequence that started with **19**, was opened by the urethane nitrogen under Lewis acid activation (BF_3 etherate)[20] and compound **29** was in hand.

In summary, we have shown the viability of a synthetic strategy organized around the central idea of using an oxetane linkage to store molecular functionality in a compact setting. In this case, the logic was used to deliver a highly hindered hydroxymethyl function. Key selectivity issues with potentially broader ramifications in synthesis were resolved favorably in the regioselective hydroboration of **13** and in the stereoconvergent rearrangements of **23** and **24**→**26**. The progression of **29** to gelsemine, requiring responses to some difficult and unanticipated challenges, is described in an accompanying paper.



Scheme 3. Construction of quaternary C7 and the pyrollidine ring. *Reagents and conditions*: (a) TFA/CH_2Cl_2, 0°C, 81%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 81%; (c) triethylphosphonoacetate, NaH, THF, 0°C, 3:2, 92%; (d) DIBAL, CH_2Cl_2, −78°C, 88%; (e) cat. propionic acid, $H_3CC(OEt)_3$, toluene, reflux, 64%; (f) NaOH/THF/EtOH, 86%; (g) diphenylphosphoryl azide, Et_3N, benzene, 25°C, reflux; MeOH, reflux; 89%; (h) BF_3·Et_2O, CH_2Cl_2, −78 to 12°C, 64%; (i) PivCl, Et_3N, DMAP, CH_2Cl_2, 0–25°C, 92%. DIBAL = diisobutylaluminum hydride; PivCl = 2,2,2-trimethylacetyl chloride; DMAP = *N*,*N*-dimethylaminopyridine.

Acknowledgements

This work was supported by grants from the National Institute of Health (grant HL25848). H.L. would like to thank the Texaco Foundation for a postdoctoral fellowship. We thank Dr. George Sukenick and Ms. Sylvi Rusli of the MSKCC NMR Core Facility for NMR and MS spectral analyses (NIH Grant CA08748).

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