J|A|C|S
ARTICLES
Published on Web 07/27/2002

Explorations in Organic Chemistry Leading to the Total Synthesis of (±)-Gelsemine

Fay W. Ng,[†] Hong Lin,[‡] and Samuel J. Danishefsky*[,†,‡]

Contribution from the Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, and Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, Box 106, New York, New York 10021

Received April 1, 2002

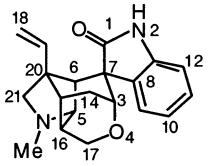
Abstract: The total synthesis of (±)-gelsemine (**1**) is described. A defining phase of the effort involved recourse to a strategic oxetane ring (see compound **25**). It was constructed anticipating an intramolecular displacement of the carbon (C17)−oxygen (O4) bond (see product **48**). A key intermediate in the stereospecific elaboration of the oxetane linkage was enone **22**, which was susceptible to two β-face attacks leading to **24** and, thence, **25**. Three sigmatropic rearrangements were employed in building the bridgehead (C20) and the spiroanilide (C7) quaternary centers en route to gelsemine.

Introduction

The earliest recorded statement of the existence of the alkaloid now called gelsemine (**1**, Figure 1) can be traced to 1870.[1] The material was isolated from *gelseminium semperverens*. More than 80 years were to elapse before gelsemine advanced from its status of orphan alkaloid to that of a substance of defined structure (see compound **1**). In arriving at what we now know to be the correct assignment of this rather complex structure, Conroy had hit upon a convergence of degradative and spectroscopically based arguments.[2a] Happily, the statement of structure as offered by Conroy was identical with that arrived at by Lovell and colleagues through the then infrequent format of X-ray crystallography.[2b]

The novel architecture of gelsemine did not go unnoticed by the community of organic chemists. In time, this intriguing structure began to attract the attention of many groups seeking stimulating targets for total synthesis. The interest which gelsemine engendered in synthesis-directed laboratories may seem anomalous in the context of the rather fragmentary and undocumented allusions as to its potentially useful biological properties.[3] Rather, it was the perceived opportunities for learning about chemistry through its novel structure which drove the multicenter commitment to its total synthesis.[4]

Our own relatively recent involvement in this problem arose from a perception as to how gelsemine might be fashioned in a laboratory, though we could not confidentially anticipate the outcomes to some key issues requiring favorable disposition. Accordingly, a gelsemine-directed total synthesis venture would provide a setting for exploration of significant questions.



gelsemine (**1**)

Figure 1.

Retrosynthetic Analysis

We noted that C7 is the only stereogenic center which could, in principle, be permuted while retaining the connectivities of gelsemine.

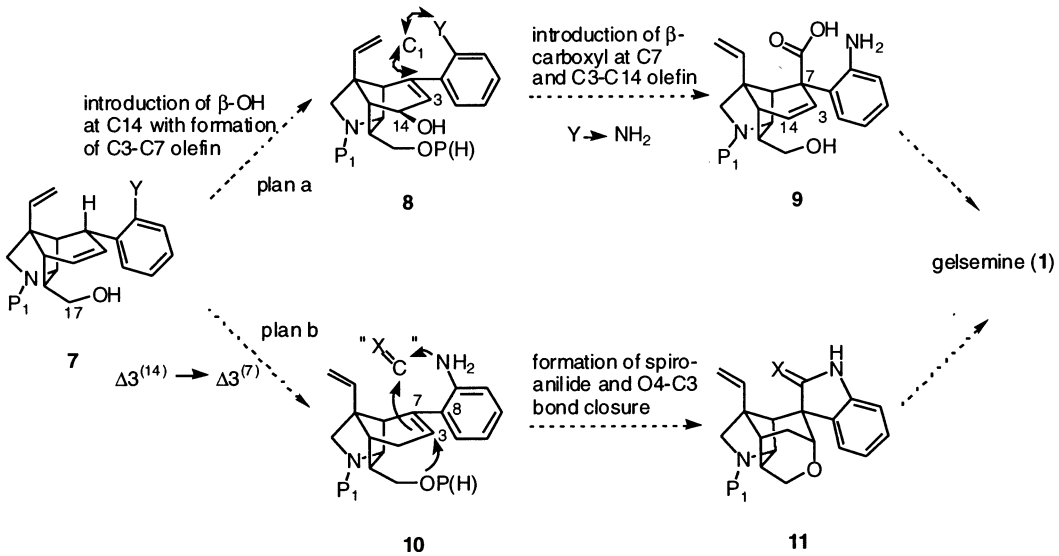
Thus, we commence our analysis at this spiro center. Formal "retro-hydrolysis" of the lactam linkage, as well as elimination of the endo face ether linkage (C3−O4), takes one back to

* Author to whom correspondence should be addressed. E-mail: s-danishefsky@ski.mskcc.org.
† Columbia University.
‡ Sloan-Kettering Institute for Cancer Research.

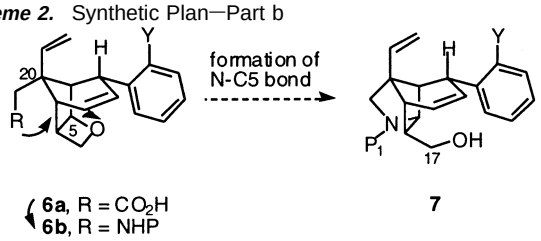
(1) Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, pp 93−117.
(2) (a) Conroy, H.; Chakrabarti, J. K. *Tetrahedron Lett.* **1959**, 6−13. (b) Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. *Tetrahedron Lett.* **1959**, 1−5.
(3) Liu, Z.-J.; Lu, R.-R. In *The Alkaloids*, Manske, R. H. F., Ed.; Academic Press: New York, 1988; Vol. 33, pp 83−140.
(4) For the total syntheses of gelsemine (**1**), see: (a) Newcombe, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767−768. (b) Sheikh, Z.; Steel, R. W.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 763−764. (c) Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765−766. (d) Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226−6241. (e) Kuzmich, D.; Wu, S. C.; Ha, D.-C.; Lee, C.-S.; Ramesh, S.; Atarashi, S.; Choi, J.-K.; Hart, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6943−6944. (f) Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427. (g) Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4073−4075. (h) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2934−2936. (i) Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 545−548. (j) Lin, H.; Ng, F. W.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 549−551. For the synthetic studies towards gelsemine (**1**), see: (k) Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett.* **1987**, *28*, 1035−1038. (l) Clarke, C.; Fleming, I.; Fortunak, J. M. D.; Gallagher, P. T.; Honan, M. C.; Mann, A.; Nübling, C. O.; Raithby, P. R.; Wolff, J. J. *Tetrahedron* **1988**, *44*, 3931−3944. (m) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561−562. (n) Avent, A. G.; Byrne, P. W.; Penkett, C. S. *Org. Lett.* **1999**, *1*, 2073−2075.

10.1021/ja0204675 CCC: $22.00

Scheme 1. Synthetic Plan—Part a



Scheme 2. Synthetic Plan—Part b



structure **9**. A less obvious prospectus led to excision of the carboxyl function of **9** and its replacement by an allylically transposed β-hydroxyl group at C14 (see structure **8**). Progress in the forward sense requires introduction of a one-carbon fragment at C7 and its bridging to an anilino nitrogen. Two broad possibilities were envisioned to achieve such a goal. Guidance for the proposed introduction could be provided by the β-disposed hydroxyl at C14 via a suprafacial sigmatropic rearrangement of a suitably activated derivative (for the moment unspecified) of the C14 allylic alcohol (plan a, Scheme 1).

A more novel possibility contemplates the introduction of a β-face C1 unit at C7 *using coordinated guidance from the C17 hydroxyl on the underface of the molecule, and the β-disposed Y function* (plan b, **10** → **11**). As will be seen, realization of the overall formal progression of **8** → **9** was accomplished by a step-intensive variation of plan a.

Significant thought was given to the installation of the two hydroxyl-level groups in **8**. It seemed that the C14 allylic alcohol in **8** could be fashioned from either $\Delta 3^{(7)}$ or $\Delta 3^{(14)}$ olefins by, overall, two-electron oxidation. The $\Delta 3^{(14)}$ olefin was selected because **8** was seen to be accessible by an interesting planned rearrangement (vide infra).

Providing for the hydroxymethyl group (see C17 alcohol) residing in the concave and highly congested space of the system. The underside (α face) of **7** is quite hindered, and we sensed potentially serious difficulties in the conduct of multiple late-stage operations in this concave domain.

These apprehensions prompted an intriguing possibility. We came to envision an intramolecular displacement of a properly configured oxetane (see sequence **6** → **7**, Scheme 2) as a key step. *In this way, the required C17 hydroxymethyl group is released as the pyrrolidine ring is established.*

In thinking about access to the sorts of electrophilic oxetane—proximal nucleophile combinations, it was proposed that the nucleophilic arm of the projected oxetane displacement reaction be a urethane linkage insulated from C20 by a single methylene group. This ureidomethyl group would have arisen from a Curtius degradation of a suitable two-carbon carboxylic acid, mounted at C20 (see structures **6a** and **6b**).

This line of thinking prompted conjectures about the possibility of *concurrent presentation of the C20 vinyl group and the acetic acid residues in **6a** via some form of a [3,3] rearrangement*. The face selectivity issues in a transformation of the type **5** → **6a** would be still another question worthy of exploration. Assuming that 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**, Scheme 3). The oxetane moiety in **5** would be fashioned from a C5—C16 olefinic linkage by an overall addition of a "formaldehyde" residue in the proper regiochemical and stereochemical senses via **4** (vide infra), thereby raising questions which were key to our proposal.

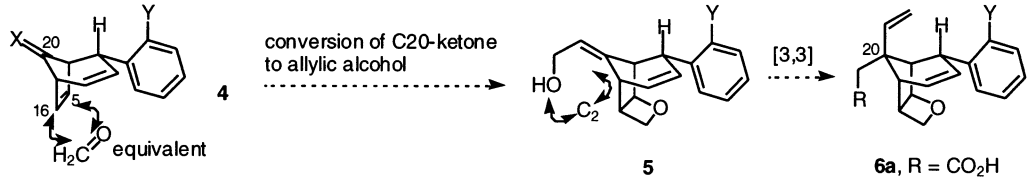
To anchor this scheme to a specific chemical substance known in the literature, we envisioned still another sigmatropic bond reorganization process. Thus, **4** might well be derived from a divinyl cyclopropane → cycloheptadiene rearrangement (**3** → **4**). Compound type **3** could be reached by chain extension (cf. *o*-nitrobenzylidenation) of the aldehyde linkage of the known substrate, **2**,[6] thereby completing the formal proposal in closed form (Scheme 4). As will be seen, the broad vision of the problem presented above was ultimately realized. However, many surprises were to await us, each presenting its own learning opportunity.

Discussion of Results

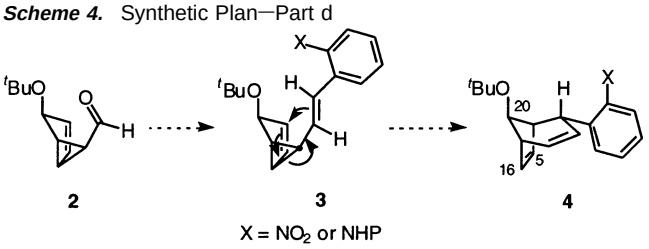
Establishment of the Key Oxetane via a Hydroboration Reaction under Homoallylic Guidance. The synthesis commenced with the epoxidation of 7-*tert*-butoxynorbornadiene

(5) 7-*tert*-Butoxynorbornadiene is commercially available. It can be prepared by the method of Story: Story, P. R. *J. Org. Chem.* **1961**, *26*, 287—290.
(6) (a) Klumpp, G. W.; Barnick, J. W. F. K.; Veefkind, A. H.; Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 766—778. (b) Cupas, C.; Watts, W. E.; Schleyer, P. v. R. *Tetrahedron Lett.* **1964**, 2503—2507.

Scheme 3. Synthetic Plan—Part c



Scheme 4. Synthetic Plan—Part d



(Scheme 5).[5] Alumina-promoted rearrangement of the epoxide afforded the known aldehyde **2**.[6] We hoped to exploit the projected divinylcyclopropane → cycloheptadiene rearrangement (cf. **2** → **4**) to fashion a system wherein the aryl group would be well developed to service spiroanilide formation at C7. To maximize our options in this regard, we favored initial recourse to an *o*-nitrophenyl group at C7 of the product.[7] In the event, the desired **14** was obtained in one step, presumably via the intermediacy of Cope precursor **13**, as shown. In principle, oxetane precursor **16** could be readily obtained from alcohol **15a**. The latter might be reached from **14** via the classical Brown hydroboration−oxidation sequence.

Such a projected hydroboration reaction clearly confronts the question of chemoselectivity between the olefinic centers. It was hoped that the greater level of strain of the C5−C16 double bond, relative to the C3−C14 site, would increase the susceptibility of the former to the action of well-selected hydroborating agents. While the facial sense of attack at the C5−C16 unsaturation was not, per se, important since we would be oxidizing the alcohol function in **15a** to ketone **16**, we anticipated (and soon confirmed) that attack of external agents on **14** would occur from its convex surface with high selectivity, thus avoiding a potential awkwardness of stereomixtures.

Of course, the key issue was the sense of regiopreference of the expected attack at the C5−C16 locus of unsaturation. The well-known suprafaciality which governs the topography of hydroboration reactions is most readily accommodated by a synchronous delivery of the H and the boron to the double bond (see Figure 2, structure **i**). *However, this synchroneity at the stereochemical level does not preclude influencing the regiochemistry of this reaction by appropriate biasing forces*. Indeed, one of the original milestones in terms of the synthetic value of hydroboration reactions arose[8] from their strict anti-Markownikov character (see **i** → **ii**). Thus, even in the synchronous mode, the more sterically demanding boron tends to attack the less substituted carbon of the olefin. Similarly powerful directing effects have been noted from olefins bearing potentially strongly electron-donating groups (see olefin **iii**), giving rise to hydroboration products of the type **iv**. Of course, it would be difficult to distinguish, in a convincing way, the overall polar contributions to the outcome from steric forces since both effects converge in predicting the formation of **iv**.

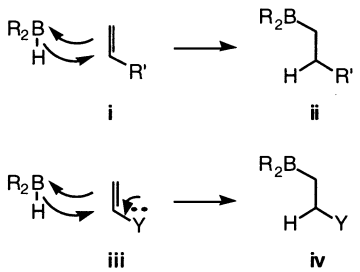


Figure 2. Steric and electronic effect in hydroboration.

There were two a priori considerations that made the issue of hydroboration of **14** particularly interesting. First, the steric forces biasing attack at one carbon or another would appear to be minimal at best. Hence, such a reaction on **14** would serve to focus on the question of the effects of electronic influences, even when uncomplicated by steric bias, in hydroboration. Moreover, the polar influences would be quite subtle. In the case at hand, a potential factor favoring directivity of the reaction in the desired sense would be the C3−C14 double bond. A bias might arise for attack in the desired sense at C5 through the intercession of homoallylic stabilization of the putative entity arising in the non fully concerted hydroboration (see arrows in **14**).

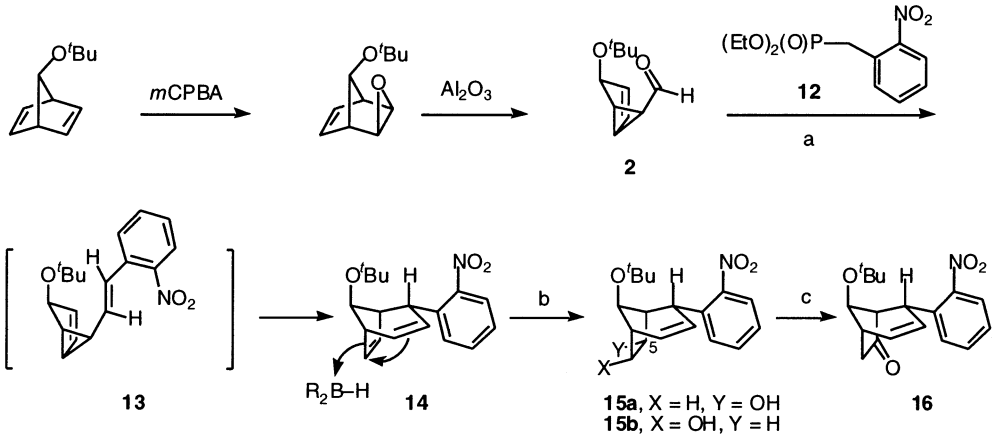
In the event, treatment of **14** with BH_2Cl·DMS followed by oxidative workup, as shown, afforded an 11:1 ratio of alcohol **15a** with the newly introduced alcohol at C5, relative to its isomer **15b**, where the alcohol is at C16. Oxidation, as shown, led to ketone **16**. Before advancing to gelsemine, we stop to examine this hydroboration reaction in somewhat greater detail.

First, we asked the question as to the effects of modifying the electrophilicity of the hydroborating entity. Intuitively, it appeared to us likely that as the attacking agent becomes more electrophilic in nature, the homoallylic stabilization effect could well be more pronounced. The question was posed in the context of olefin **17**[9] bearing a phenyl rather than a nitrophenyl group on the three-carbon bridge (see Scheme 6). We note that, in using 9-BBN, the ratio of **18a**:**18b** was 6:1. *By contrast, use of the more electrophilic chloroborane DMS reagent gave rise to a more favorable ratio, 16:1*.

We next examined the consequences of modifying the aryl function. Once again, at the intuitive level it seemed likely that as the C7 bound aryl group is more electron withdrawing, even in an inductive sense, the postulated homoallylic conjugating proclivity of the double bond could be attenuated. In this connection, it was interesting to compare the hydroboration of olefins **17** and **14** (**15a**:**15b** = 11:1 using BH_2Cl·DMS).[10] Once again, the outcome was in keeping with the sorts of expectations engendered by the homoallylic stabilization argument discussed above.

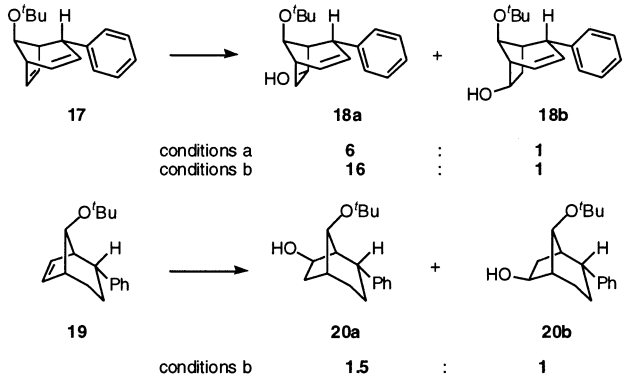
(7) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313−5320.
(8) (a) Brown, H. C. *Hydroboration*; Benjamin: New York, 1962. (b) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975. (c) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic: London, 1988.
(9) Ng, F. W.; Chiu, P.; Danishefsky, S. J. *Tetrahedron Lett.* **1998**, 767−770.
(10) See details in Dr. Fay W. Ng's thesis: Ng, F. W. Ph.D. Thesis, Columbia Unversity, 1997.

Scheme 5 [a]



[a] Conditions and reagents: (a) **11**, LiHMDS, −10 °C, 71%; (b) BH_2Cl·DMS, Et_2O, 0 °C; $NaOH/H_2O_2$, 77%, +7% regioisomer; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 99%.

Scheme 6. Study of Regioselectivity of Hydroboration[a]



[a] Conditions and reagents: (a) 9-BBN, THF, 0−25 °C; $NaOH/H_2O_2$; (b) BH_2Cl·DMS, Et_2O, 0 °C; $NaOH/H_2O_2$.

In a key experiment, we examined the behavior of olefin **19** wherein the double bond in the three-carbon bridge had been deleted through reduction. Interestingly, hydroboration with monochloroborane gave rise to a 1.5:1 mixture of alcohols **20a** and **20b**, respectively. Thus, it seems clearly that the regiopreference for attack at C5 in olefin **14** is directly tied to participation of the C3−C14 olefinic site. Similar findings described elsewhere were recorded in the context of oxymercuration of olefins **17**.[9]

We now return to the total synthesis of gelsemine starting with ketone, **16**. As it turned out, some chemistry we had conducted in 1975 provided the basis of the next few steps.[11a,b] Thus, **16** could be converted to its silyl enol ether, which was treated with the Eschenmoser salt (CH_2=NMe_2I)[11c] to afford dimethylaminomethylene ketone **21**[12] (see Scheme 7).

Following quaternization of the nitrogen and β-elimination, the α-methyleneketone, **22**, was in hand. *At this stage we were able to take advantage of two β-face addition reactions to control progression of the sp² carbon centers C5 and C16 to the sp³ level of hybridization*. In the event, hydride delivery at C5, in the context of a Luche reaction,[13] afforded **23**. In a similar vein, hydroboration followed by oxidation of **23** also occurred from the β-face, generating diol **24**.[14] From this diol intermediate, the primary hydroxy group was selectively activated as the mesylate, which was displaced by the oxy anion to fashion the α-face oxetane (**25**) in a straightforward manner (see Scheme 7).

Construction of the Bridgehead Quaternary Center and the Pyrrolidine Ring. 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**. As alluded in Scheme 3, we would be anticipating a [3,3]-type rearrangement en route to structure type **6**. Following the cleavage of *tert*-butyl ether **25**,[15] the resulting alcohol function in **26** was oxidized to afford ketone **27** (Scheme 8). Horner−Wadsworth−Emmons (HWE) condensation[16] of the ketone function was successful in terms of overall yield but led to a 3:2 mixture of β,β-disubstituted stereoisomers **28a** (*Z* isomer) and **28b** (*E* isomer). Each of these compounds was converted by reduction to its allylic alcohol counterpart (**29a** and **29b**, respectively).[17] These isomers were individually treated with triethylorthoacetate as shown.[18] Remarkably, each allylic alcohol gave rise to a single and identical γ,δ-unsaturated ester **31** (presumably via **30**) with the β-vinyl and α-carboxymethyl functions at C20 as required for the synthesis.[19]

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 the oxetane (see **30** → **31**).

We first hypothesized that the facial selectivity of **29a** (*Z* isomer) might arise from a steric effect of the axial proton at C7. The facial selectivity of **29b** (*E* isomer) might arise from

(11) (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 899−912. (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028−3030. (c) Kleinman, E. F. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 3, pp 2090−2093.

(12) The stereochemistry of C16 of **21** was not determined.

(13) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976−977.

(14) It was unlikely for the hydroboration to occur on the endo face, presumbably because the free hydroxyl group reacted with the boron reagent to give the boronate ester, which is a poor chelating partner. See: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(15) Beyerman, H. C.; Heiszwolf, G. L. *J. Chem. Soc.* **1963**, 755−756.

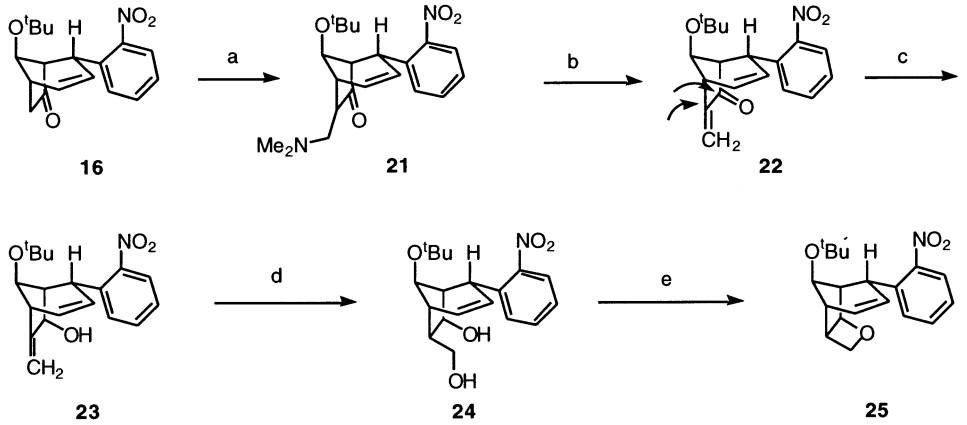
(16) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(17) Winterfeldt, E. *Synthesis* **1975**, 617−630.

(18) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brosksom, T. J.; Li, T.-T.; Faulkner, D. J.; Perterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743. For an overview of Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227−232.

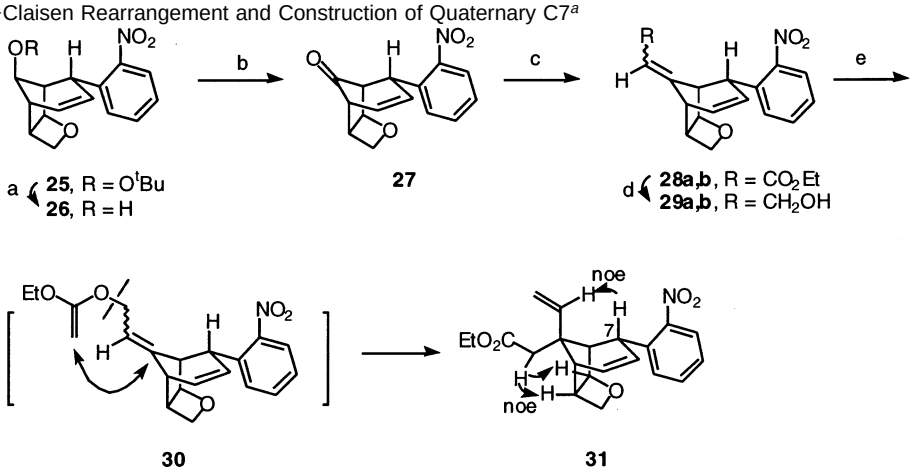
(19) After this discovery, the 3:2 mixture of allylic alcohols **29a** and **29b** was subjected to the above variant of Claisen rearrangement conditions without further separation of the two isomers.

Scheme 7. Synthesis of the Oxetane Ring[a]



[a] Conditions and reagents: (a) LiHMDS, TESCl, Et_3N, THF, −78 to 0 °C; Eschenmoser's salt, CH_2Cl_2, 91%; (b) MeI, CH_2Cl_2/Et_2O; Al_2O_3, CH_2Cl_2, 95%; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 99%; (d) 9-BBN dimer, THF; $NaOH/H_2O_2$, 88%; (e) MsCl, Et_3N, CH_2Cl_2, −78 °C; NaHMDS, THF, −78 to 0 °C, 91%.

Scheme 8. Johnson−Claisen Rearrangement and Construction of Quaternary C7[a]



[a] Conditions and reagents: (a) TFA/CH_2Cl_2, 0 °C, 81%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 81%; (c) triethyl phosphonoacetate, NaH, THF, 0 °C, 3:2, 92%; (d) DIBAL, CH_2Cl_2, −78 °C, 88%; (e) $CH_3C(OEt)_3$, catalytic propionic acid, toluene, reflux, 64%.

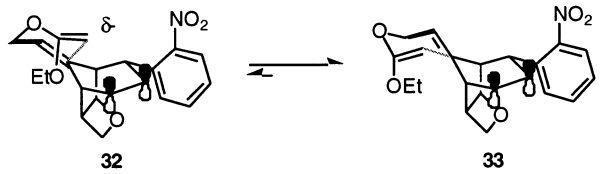


Figure 3. Electrostatic effect in facial selectivity of Claisen rearrangement.

an intriguing electronic effect, possibly of electrostatic origin,[20,21] i.e., from repulsion of the enolate-like migrating group by the C3−C14 π system. Viewed in these terms, transition state **32** is disfavored relative to **33** (see Figure 3). Still another factor operating in the same direction might be that the migrating enolate-like group is attracted to the strained and electron-withdrawing C5−C16 bond.

Additional cases were evaluated on the substrates closely related to **29** to distinguish between possible steric and electronic factors in directing the face selectivity of the migration step (see Scheme 9). HWE reaction of **34**[22] afforded a 1:3.5 mixture of **35a** and **35b**, which were separated and reduced to **36a** and **36b** with DIBAL. These isomers were individually subjected to the action of triethyl orthoacetate to afford a single rearrangement product, **37**. In this case, we argue that a steric effect arising from the lesser hindrance of the cyclopentenyl face had prevailed. The more remarkable observation arose from the rearrangements of **40a** and **40b**, where the double bond on the three-carbon bridge is styrene-like. HWE reaction of **38**[23] afforded a 2:3 mixture of **39a** and **39b**. These products were separated and individually reduced to allylic alcohols **40a**[24] and **40b**. The *Z* isomer (**40a)** was subjected to Johnson−Claisen rearrangement conditions to give a single product (**41a**) in which the migration occurred from the two-carbon face, while the *E* isomer (**40b)** was subjected to Johnson−Claisen rearrangement conditions to give a single product (**41b**) in which the migration occurred from the face of the three-carbon bridge.

This result could be explained by the electrostatic interaction between the highly polarized C7−C3 olefin and the electron-rich enolate. Perhaps in transition state **42**, arising from **40b**, the electronegative enolate terminus is closer to the electropos-

(20) For an example of the electrostatic effect observed in [3,3]-sigmatropic rearrangements, see: Kahn, S. D.; Hehre, W. J. *J. Org. Chem.* **1988**, *53*, 301−305 and references therein. For an example of the electrostatic effect observed in Diels−Alder reactions, see: Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1986**, *27*, 6041−6044. For an example of the electrostatic effect observed in nitrile oxide cycloadditions, see: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880−3882.

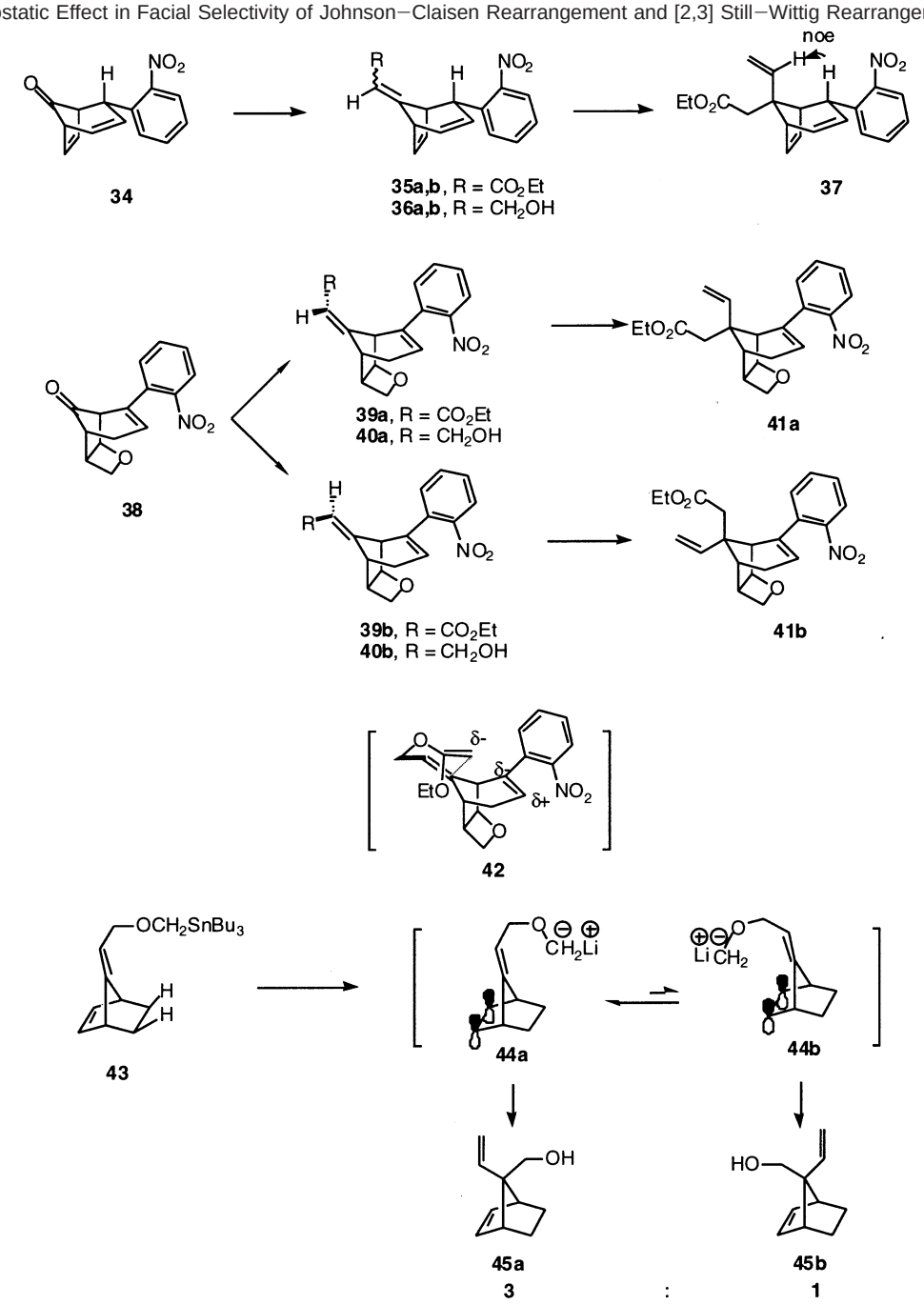
(21) Mukherjee, A.; Wu, Q.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3271−3274.

(22) Compound **34** was prepared by the cleavage of the *tert*-butoxyl group of **14** followed by Swern oxidation of the resulting alcohol.

(23) Compound **38** was prepared by the bromination of oxetane **25** followed by the reductive debromination with Ph_3SnH.

(24) The stereochemistry of **40a** was confirmed by X-ray crystallography.

Scheme 9. Electrostatic Effect in Facial Selectivity of Johnson−Claisen Rearrangement and [2,3] Still−Wittig Rearrangement



itive end (C3) of the olefin. Hence, the interaction favors the formation of product **41b**. By contrast, in the transition state of **40a**, the enolate is closer to the electronegative end (C7) of the olefin. Hence, the rearrangement occurs from the face of the two-carbon bridge to afford **41a**. In this case, clearly very subtle electronic effects control the facial selectivity.

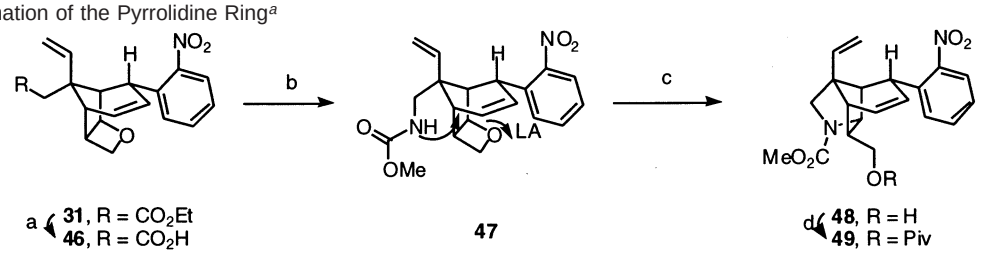
A similar electronic effect was suggested to be operative in the context of a [2,3] Still−Wittig rearrangement of **43** (see formation of **45a**:**45b** in a 3:1 ratio). It is tempting to propose that, here also, a disfavoring electrostatic repulsion between the migrating dianion ($^{-}OCH_2^{-}$) version of methanol and the alkene linkage directs the reaction along the more hindered ethano, rather than etheno, surface.

Obviously, the studies described above are suggestive rather than exhaustive. However, they point to some unprecedented and intriguing possibilities for control of face selectivity by subtle electronic factors. Remarkably, these effects may, in some cases, be more powerful than the steric hindrance paradigm, which has dominated the rationalization of problems in face selectivity.

We now return to the focusing objective, i.e., the total synthesis of gelsemine commencing with saponification of ester **31** (see formation of **46**, Scheme10).[25] The carbonyl function, upon Shiori's one-step version of the Curtius rearrangement, gave rise to the required ureido group (see compound **47**).[26] The governing plan involved closing the pyrrolidine ring by

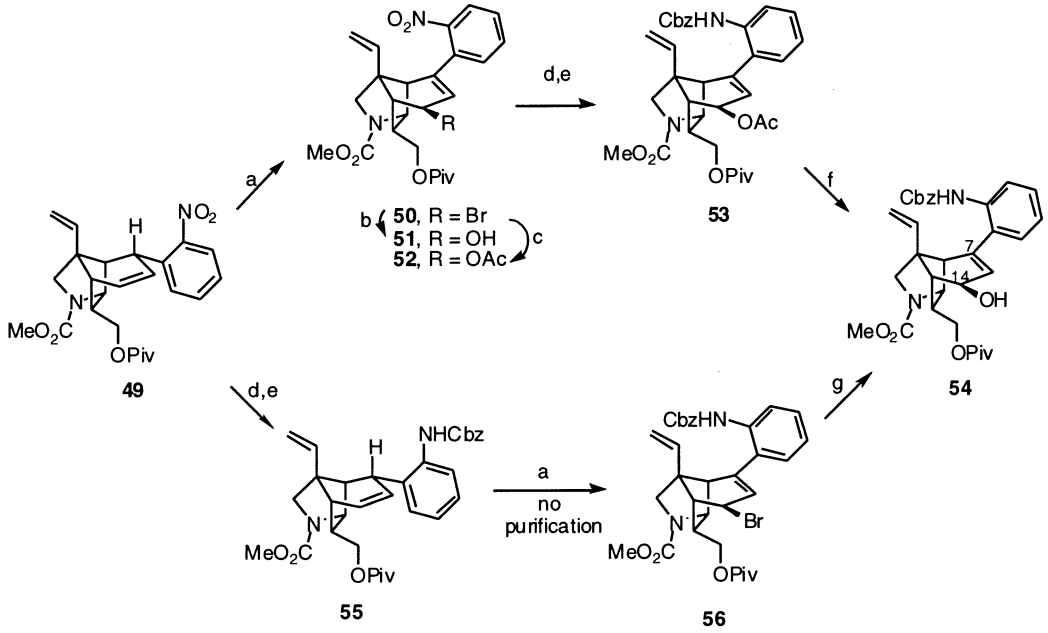
(25) Honda, M.; Hirata, K.; Sueoka, H.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1981**, *22*, 2679−2682.
(26) (a) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205. (b) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151−2152.

Scheme 10. Formation of the Pyrrolidine Ring[a]



[a] Conditions and reagents: (a) NaOH/THF/EtOH, 86%; (b) diphenylphosphoryl azide, Et_3N, benzene, reflux; MeOH, reflux; 89%; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 to 12 °C, 64%; (d) PivCl, Et_3N, DMAP, CH_2Cl_2, 0−25 °C, 92%.

Scheme 11 [a]



[a] Conditions and reagents: (a) NBS, AIBN, *hν*, CCl_4/CH_2Cl_2, 55−60 °C, 60% based on recovered starting material; (b) AIBN, Bu_3SnH, dry air, *hν*, toluene, 60 °C; $NaBH_4$, 0 °C; 55% based on recovered starting material; (c) AgOAc, HOAc, 52%; (d) zinc dust, THF/HOAc; (e) CbzCl, $NaHCO_3$, CH_2Cl_2, 94% for two steps; (f) K_2CO_3, MeOH, 90%; (g) Ag_2O, CF_3CH_2OH/H_2O, 65% for two steps.

displacement of the C5−O4 bond. Happily, the hitherto robust oxetane linkage, which had survived the sequence that started with **25**, could now be activated upon treatment with BF_3 etherate.[27] Displacement of this bond by the urethane nitrogen under these conditions provided **48**. The 17-hydroxyl group was protected as its pivaloate (see compound **49**).

Introduction of C1 via Eschenmoser−Claisen Rearrangement. As noted in Scheme 1, two plans were considered to reach penultimate intermediate type **11** (see plans a and b). They were both pursued. We start with plan a, which postulated that **49** be oxidized with allylic transposition to reach **51**. It was envisioned that a *β*-hydroxyl at C14, so introduced, could be used to direct a function to the *β*-face of C7, which would be valuable for spiroanilide formation. A key element, which accomplished overall isomerization (i.e., conjugation) of the double bond to the $\Delta3^{(7)}$ series, was allylic bromination of a $\Delta3^{(14)}$ double bond isomer. In this way, a *β*-bromine would be introduced at C14 with reappearance of the double bond at the $\Delta3^{(7)}$ position.[28] In the event, allylic bromination could be carried out on pivaloate **49**, thereby affording **50** (Scheme 11).[29] Debromination of **50** (tri-*n*-butyltin hydride) in the presence of O_2, followed by the reduction of the resulting hydroperoxide with sodium borohydride, indeed afforded **51** with high stereo- and regioselectivity.[30] Alternatively, acetolysis of **50** was accomplished, with silver acetate in acetic acid, to provide **52**.[31] The overall stereochemical retention result in this reaction attests to the highly hindered nature of the α-face at the C14 position of **50**. Reduction of the nitro group afforded the amine, which was protected with CbzCl to provide **53**. Deprotection of the acetate afforded **54**. To improve the efficiency of bromination and hydroxylation sequence, the nitro group of **49** was reduced to the aniline, which was protected with CbzCl to provide **55**. In this way, the benzylic position (C7) was easier to be oxidized. Indeed, bromination of **55** under the same conditions took place more rapidly than that of **49**. Without purification, allylic bromide **56** was treated with Ag_2O in a mixed solvent, 1:1 CF_3-

(27) Boron trifluoride was the superior Lewis acid for the activation of oxetane derivatives with intramolecular etheral oxygen participation. See: Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* **1994**, *38*, 2165−2169. Boron trifluoride catalyzed the nucleophilic ring opening of oxetane derivatives, see: Xianming, H.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1399−1408.

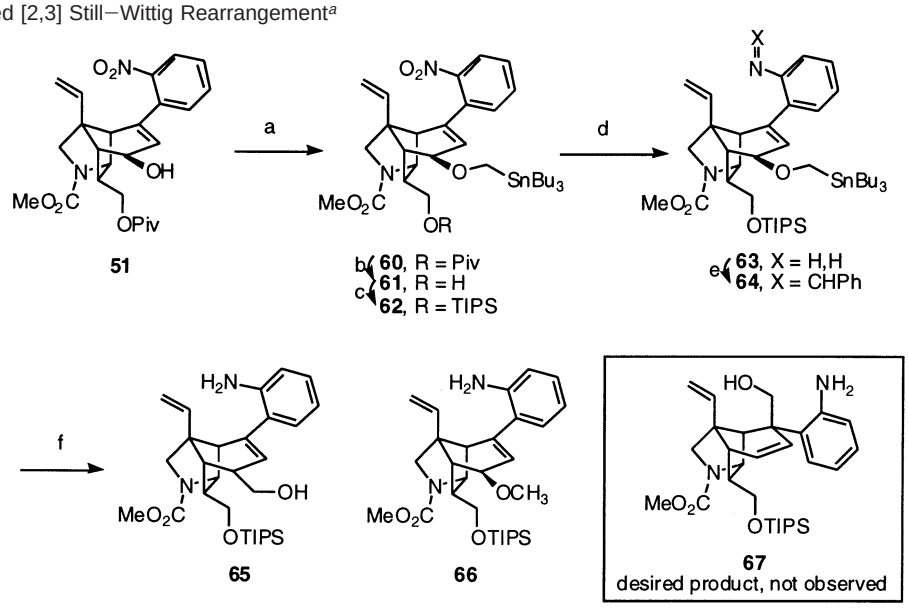
(28) For free radical benzylic bromination of substituted nitrotoluene derivatives with NBS, see: Mataka, S.; Kurisu, M.; Takahashi, K.; Tashiro, M. *Chem. Lett.* **1984**, 1969−1972.

(29) Following precedents, methylene chloride was used to minimize double bromination. See: Offermann, W.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 464−465.

(30) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980−8982. For additional examples of free-radical-initiated oxygenation, see: Mayer, S.; Prandi, J. *Tetrahedron Lett.* **1996**, *37*, 3117−3120. Moutel, S.; Prandi, J. *Tetrahedron Lett.* **1994**, *35*, 8163−8166.

(31) Cf.: Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2787−2790.

Scheme 12. Attempted [2,3] Still−Wittig Rearrangement[a]



[a] Conditions and reagents: (a) NaHMDS, 15-C-5, ICH_2SnBu_3, THF, −78 to 0 °C, 65%; (b) DIBAL, CH_2Cl_2, −78 °C, 80%; (c) TIPSOTf, Et_3N, CH_2Cl_2, 94%; (d) SmI_2, THF, MeOH, 89%; (e) PhCHO, $MgSO_4$, Et_3N, CH_2Cl_2, quantitative; (f) *n*-BuLi, THF, −78 to 25 °C.

CH_2OH/H_2O.[32] This protocol afforded **54** in 65% yield over two steps.

With compound **54** securely in hand, attentions were directed toward accomplishing the introduction of the one-carbon fragment required to bridge C7 and the anilino nitrogen. In this way, we hoped to construct the lactam with the properly configured C7 spiro center. In rough terms, what we planned was the advancement, by some means, of **57** → **58** (see Figure 4). Cyclization to the lactam and removal of the pivaloyl blocking group, also in some unspecified order, would liberate the primary alcohol at C14 (see **59**). While the precise characters of X and P′ are unspecified, previous work in the field suggests that the ring closure to establish the tetrahydropyran ring should be possible and was, in fact, accomplished in the 21-oxo series (X = O).[4a,f]

To the best of our knowledge, there is no known way in which the transformation type **57** → **58** can be accomplished in one step.

We first explored the possibility of a [2,3] Still−Wittig rearrangement[33] to introduce a hydroxymethyl group at C7 with allylic transposition. The result was disappointing (Scheme 12). *O*-Alkylation of alcohol **51** with iodomethyltributyltin in the presence of 15-crown-5 afforded α-stannylmethyl ether **60**. Attempts at [2,3]-sigmatropic rearrangements were unsuccessful, probably due to the incompatibility of the nitrophenyl group and *n*-BuLi used in the reductive initiation.[34] The pivaloate protection of **60** was also replaced by a TIPS ether (**60** → **61** → **62**) to minimize potential complications in the use of BuLi for triggering the rearrangement. In the event, nitroarene **62** was reduced with SmI_2 to produce aniline **63**. The amine was

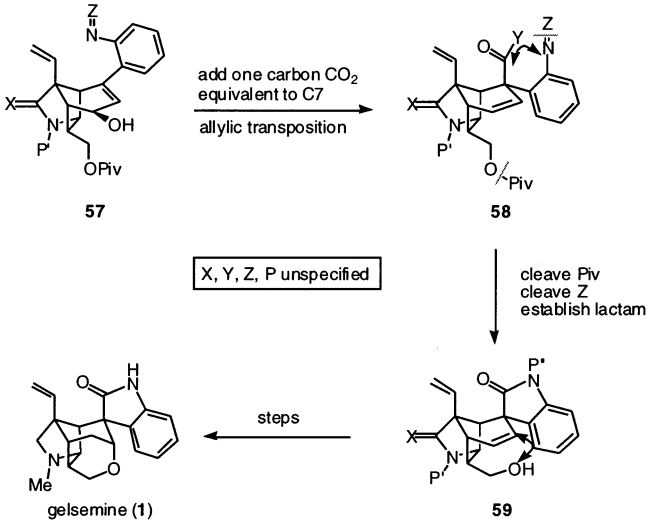


Figure 4. Synthetic plan for construction of the spiro-oxindole and the tetrahydropyran motif.

protected as a Schiff base (see compound **64**). Unfortunately, neither **63** nor **64** underwent the rearrangement in a [2,3] fashion to give the desired product **67**. The only detected products were homoallylic alcohol **65**[35] via [1,2] rearrangement[36] from aniline **63** or a mixture of **65** and **66** from Schiff base **64**.

We next sought to accomplish a Büchi rearrangement[37] of allylic alcohol **54** mediated by *N,N*-dimethylformamide dimethyl acetal. This attempt also failed to provide either the desired amide **69** or cyclized oxindole **70** (Scheme 13). Remarkably, under the pyrolytic conditions, a mixture of compounds assigned to be *N*-benzyloxycarbonyl-*o*-quinone methide imines **68a** and **68b** was obtained.[38] Because the ^1H NMR spectrum of **68a** and **68b** was complicated by the presence of rotamers, the ratio of these two isomers remained undetermined.[39] Treatment of the

(32) For an example using CF_3CH_2OH as the solvent for hydrolysis of benzylic bromides, see: Steenkamp, J. A.; Malan, J. C. S.; Ferreire, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2179−2183.

(33) For an overview of [2,3] Wittig rearrangements, see: (a) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105−209. (b) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885−902.

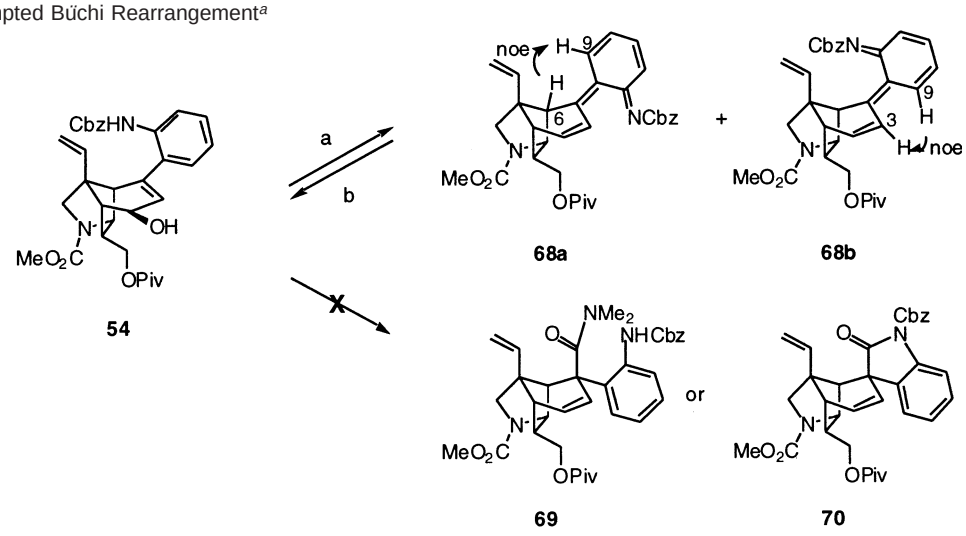
(34) Nitrobenzene has been employed as the source of oxygen in hydroxylation of aryllithium derivatives at low temperature (−75 °C): Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 1941−1944. Phenyllithium reacts with nitrobenzene to give phenoxide at low temperature: Buck, P.; Kobrich, G. *Tetrahedron Lett.* **1967**, 1563−1565.

(35) The stereochemistry at C14 of the rearrangement product (**60**) was not determined.

(36) Cf.: Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927−1928.

(37) Büchi, G.; Cushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 5563−5565.

Scheme 13. Attempted Büchi Rearrangement[a]



[a] Conditions and reagents: (a) $HC(OMe)_2NMe_2$, *m*-xylene, reflux, 70−80%; (b) CF_3CH_2OH/H_2O 1:1, $TsOH\cdot H_2O$, 85%.

mixture of **68a** and **68b** with a catalytic amount of $TsOH\cdot H_2O$ in a mixed solvent, CF_3CH_2OH/H_2O 1:1, restored allylic alcohol **54** in good yield.

These setbacks suggested some serious obstacles, presumably reflecting steric hindrance issues, associated with even intramolecular construction of the C7 quaternary center. Still another effort along these lines contemplated a [2,3]-sigmatropic rearrangement to be initiated from the dithio carbenoid[40] species derived from **50** or **56**. Unfortunately, this idea could never be tested because bromide **50** failed to undergo displacement with a thio nucleophile.[41]

With considerable reluctance we abandoned the notion based on [2,3] rearrangements and turned to a [3,3] process. We were not unmindful that such a program, if reduced to practice, could introduce a two-carbon unit at C7 and would necessitate excision of the extraneous carbon. Various protocols to achieve [3,3]-sigmatropic rearrangement were examined (Scheme 14).

Unfortunately, attempted Johnson or Ireland ester enolate rearrangements on compounds **51** and **54**, respectively, were unsuccessful, leading only to recovered starting materials. Similarly disappointing were attempted Ireland ester enolate Claisen rearrangements[42] on acetate **52** or on α-substituted acetates **71a**,**b** or **72**, which failed to occur. The only reaction pathway which we could identify in these ester enolate cases was deacylation with restoration of the precursor alcohols. Once again, formidable steric forces seemed to be arrayed against even intramolecular delivery to the β-face of C7.

Fortunately, it was found that the Eschenmoser amide acetal version of the Claisen rearrangement did take place in the desired [3,3] sense.[43] In the event, subjection of **54** to the conditions shown indeed afforded **73**. The long-awaited suprafacial chirality transfer from C4 to C7 had occurred, albeit in a fashion which would require some form of degradation to reach the C7 spirolinked oxindole. Treatment of **73** with silica gel led to the formation of the δ-lactam **74**. Purification at the end of this sequence led to the detection of product **75**. Following deprotection of the pivaloate and Cbz groups, compound **76**[44] was in hand.

Interestingly, treatment of **75** with $TsOH\cdot H_2O$ in a mixed solvent, CF_3CH_2OH/H_2O 1:1, at 70 °C afforded **54** in good yield, presumably through a conjugated cation or *N*-benzyloxycarbonyl-*o*-quinone methide imine **68**.

Other Strategies Attempted for the Synthesis of the Spirooxindole. Before relating how the spirodihydroquinilone derivative **74** was converted to the spiro-oxindole following one-carbon excision, it is well to describe experiments directed to the realization of variations of plan b (see Scheme 1). While ultimately not successful in terms of our goal, these studies yielded interesting chemistry. Our initiatives were possible because we could gain access through our chemistry to the $\Delta 3^{(7)}$ double bond isomer of the type **10**. We hoped to exploit this capability for introduction of a one-carbon residue between C7 and the anilino nitrogen, with or without concurrent participation from the primary hydroxy function.

One of the strategies investigated was an oxymercuration−transmetalation−carboxylation sequence (Scheme 15). In the event, allyl bromide **50** was reduced with Ph_3SnH to provide **77** which, following deprotection of the pivaloate, led to alcohol **78**. Treatment of **78** with $Hg(OTf)_2$ led to the formation of the cyclized chloromercuric system (**79**), containing the desired tetrahydropyran moiety. Unfortunately, all attempts to accomplish introduction of a one-carbon fragment via transmetalation−carboxylation[45−47] resulted in recovery of **78**. Attempts to trap the radical intermediate from demercuration of **79** with

(38) For examples of preparations and reactions of *o*-quinone methide imines, see: (a) Ito, Y.; Nakajo, E.; Saegusa, T. *Synth. Commun.* **1986**, *16*, 1073−1080. (b) Nishiyama, K.; Kubo, H.; Sato, T.; Higashiyama, K.; Ohmiya, S. *Heterocycles* **1998**, *48*, 1103−1106.

(39) The cross-peaks between H6 and H9 (for **68a**), and between H3 and H9 (for **68b**), in the 2D NOESY spectrum of **68** indicated the existence of both isomers.

(40) For examples of [2,3]-sigmatropic rearrangement of dithio carbenoids, see: (a) Andrews, G.; Evans, D. A. *Tetrahedron Lett.* **1972**, *50*, 5121−5124. (b) Nakai, T.; Mikami, K. *Chem. Lett.* **1978**, 1243−1244. (c) Nakai, T.; Mikami, K. *Chem. Lett.* **1979**, 1081−1084.

(41) For example, no reaction occurred when bromide **50** was treated with PhS^- or PhSH in the presence of Ag(I) salts.

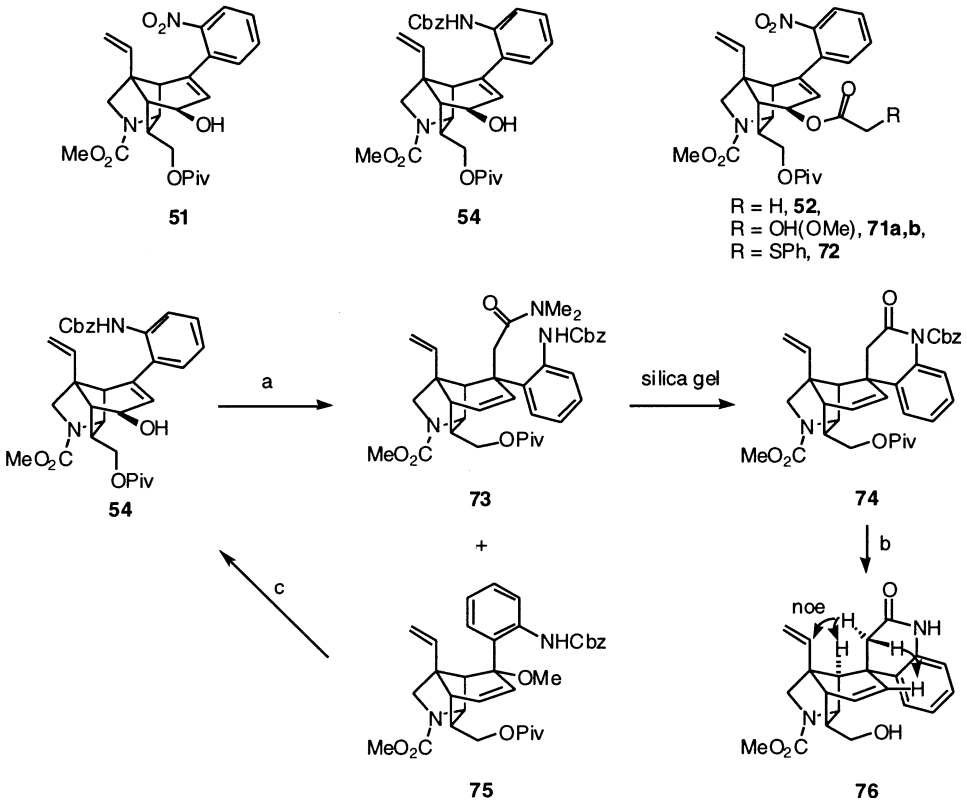
(42) For a recent review on Ireland−Claisen rearrangement, see: Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17−19.

(43) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030−1042.

(44) Compound **76** was prepared to clarify the stereo outcome of the Claisen rearrangement as shown in Scheme 14. The most conclusive signal was the NOE between one of the α-protons in the lactam and H19 (the methine proton of the terminal alkene).

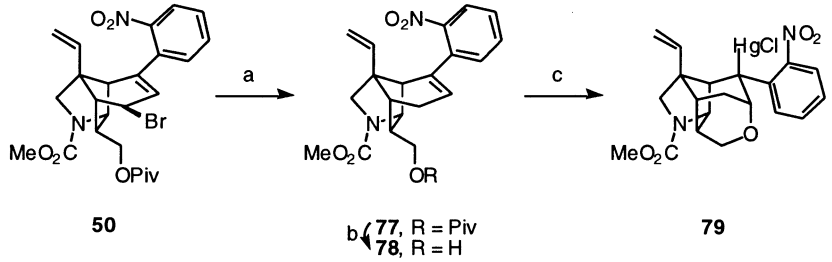
(45) For a general review on palladium(II)-assisted reactions/insertion processes involving transmetalation, see: Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415−2434.

Scheme 14 [a]



[a] Conditions and reagents: (a) $CH_3C(OMe)_2NMe_2$, *m*-xylene, 45% of **74** and 26% of **75**; (b) NaOMe, MeOH, 74%; (c) CF_3CH_2OH/H_2O 1:1, $TsOH\cdot H_2O$, 70 °C, 81%.

Scheme 15 [a]



[a] Conditions and reagents: (a) Ph_3SnH, AIBN, *hν*, toluene, 52%; (b) DIBAL, CH_2Cl_2, −78 °C, 91%; (c) $Hg(OTf)_2$, CH_2Cl_2, K_2CO_3, then saturated NaCl, 43%.

tert-butylisonitrile, with the notion of incorporating a cyano group, gave only the demercuration product.

A tandem cyclization strategy of an isocyanate intermediate was also investigated (Scheme 16). Alcohol **78** was protected as its silyl ether (see compound **80**), and the nitro group was reduced to the corresponding aniline, thereby affording **81**, which was converted to isocyanate **82**[48,49] with triphosgene.[50] It was hoped that deprotection of the silyl ether of **82** would provide an alkoxide intermediate that could participate in a 6-*exo*-*trig* cyclization to form the tetrahydropyran moiety, followed by a benzylic anionic 5-*endo*-*dig* cyclization to install the spiro-oxindole unit, providing the desired **83** containing the gelsemine skeleton. Unfortunately, what was found was that isocyanate **82** gave quinolone **84** upon standing under vacuum. While this was an undesirable result, it was not per se surprising. Thus, polyene cyclization processes in general have historically been preferentially directed toward the formation of six-membered rings over five-membered rings.[51] Moreover, in the present case, the reaction led to a six-membered lactam. We note that in the sense of the observed reaction, it led to benzylic cation-like species. Subsequent proton elimination gave quinolone **84**.

An alternative approach to the spiro oxindole moiety was to introduce an indolenine (**92**) from *o*-isonitrile styrene derivatives under free radical conditions[52] (Scheme 17). The nitro group of acetate **85** was reduced to the aniline, which was then

(46) For transmetalation with palladium(II) of an organomercurial, see: (a) Henry, P. M. *Tetrahedron Lett.* **1968**, 2285−228. (b) Kocovsky, P.; Srogl, J.; Gogoll, A.; Hanus, V.; Polasek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086−1087.

(47) For intermolecular trapping of cyclization of organomercurial, see: Kocovsky, P.; Grech, J. M.; Mitchell, W. L. *Tetrahedron Lett.* **1996**, *37*, 1125−1128.

(48) Ulrich, H.; Richter, R.; Tucker, B. *Synthesis* **1979**, 277−279.

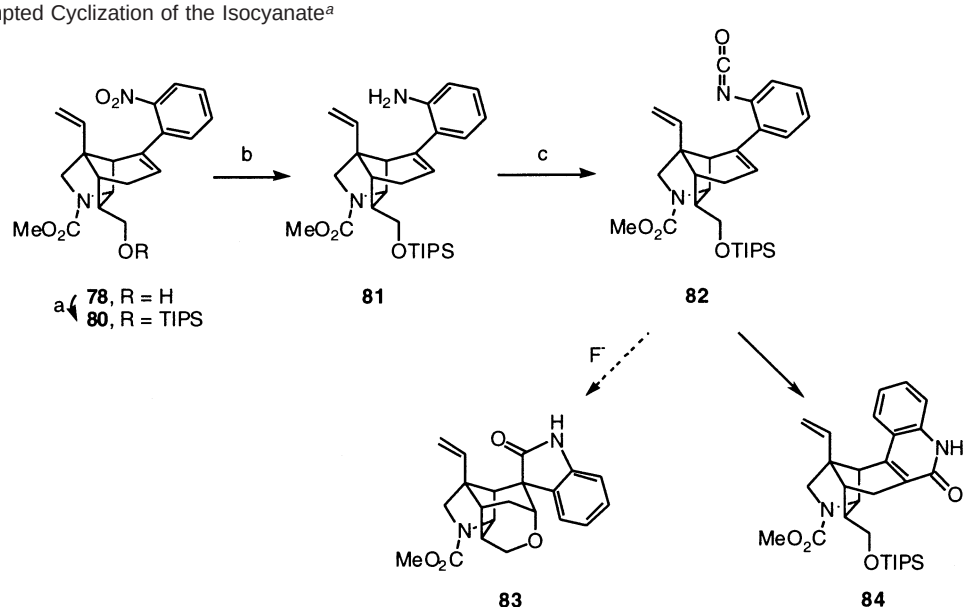
(49) The isocyanate **82** was partially visualized by IR: *ν* 2260 (isocyanate).

(50) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894−895.

(51) The propensity to form six-membered rings under cationic cyclization conditions has been amply demonstrated in polyene cyclizations. For a review, see: Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 341−377.

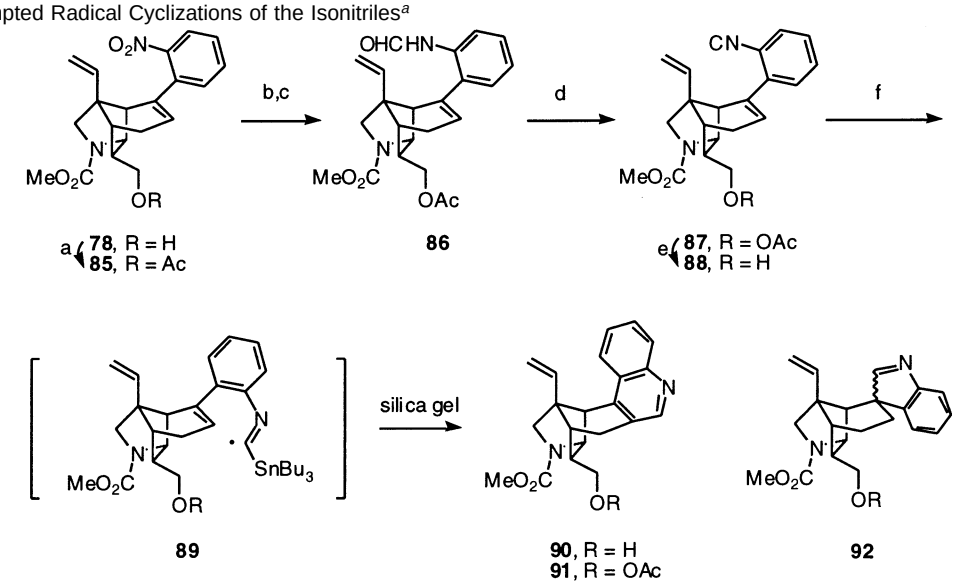
(52) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127−3128.

Scheme 16. Attempted Cyclization of the Isocyanate[a]



[a] Conditions and reagents: (a) TIPSOTf, Et_3N, CH_2Cl_2, 96%; (b) SmI_2, THF/MeOH, 71%; (c) triphosgene, EtOAc; high vacuum, 25 °C, 71%.

Scheme 17. Attempted Radical Cyclizations of the Isonitriles[a]



[a] Conditions and reagents: (a) Ac_2O, pyridine, 82%; (b) SmI_2, THF, MeOH, 91%; (c) HCO_2H, Ac_2O, 96%; (d) triphosgene, Et_3N, CH_2Cl_2, 97%; (e) NaOMe, MeOH, 87%; (f) Bu_3SnH, AIBN, CH_3CN, 100 °C, 43−60%.

formylated to afford *N*-formylanilide **86**.[53] Dehydration of **86** delivered isonitrile **87**, which was hydrolyzed to **88**. With isonitrile derivatives **87** and **88** in hand, their free radical cyclizations were pursued. However, no indolenine product **92** was detected. The observed free radical cyclization result (see compounds **90** and **91**) was interesting from a mechanistic point of view. A priori, it is conceivable that the cyclization of iminocarbon radical **89** was more favorable through a 6-*endo*-*trig* pathway. Such a path would generate a benzylic radical. From there, cyclization would lead to the observed **90**. The benzylic radical intermediates presumably suffered hydride abstraction and destannylation to afford quinolines **90** and **91**.[54]

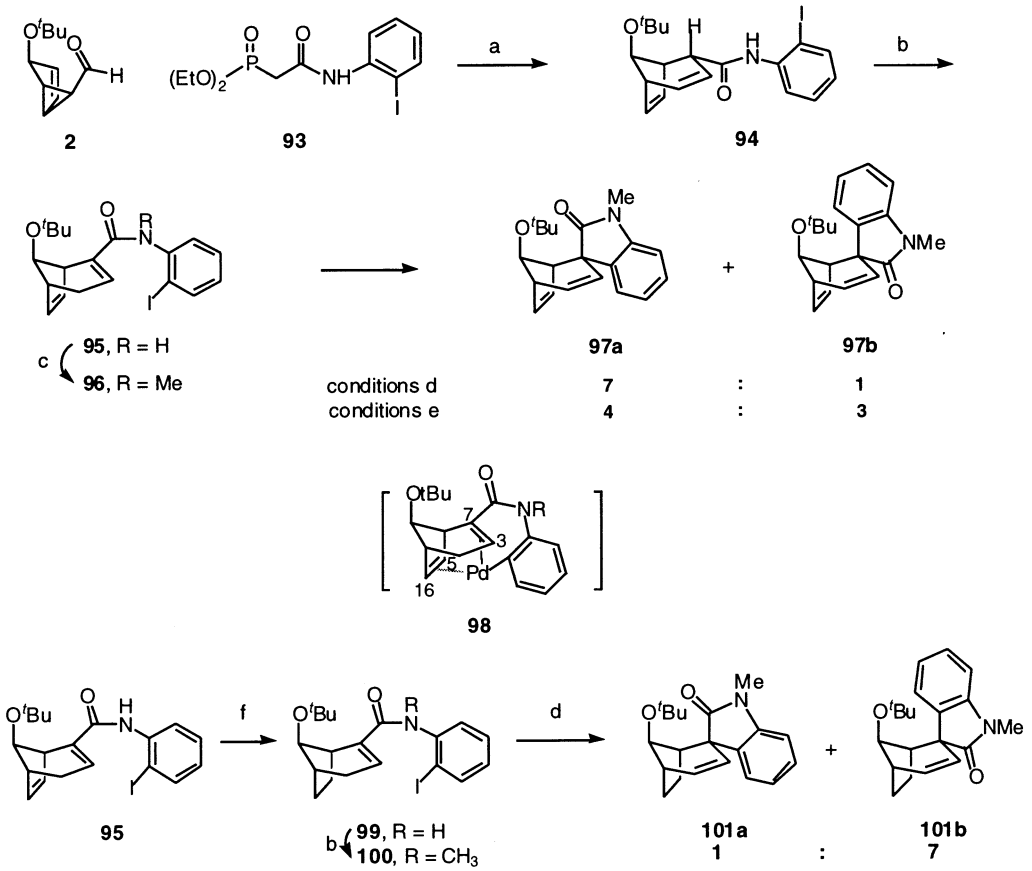
We also studied the possibility of introducing the spirooxindole at a much earlier stage of the synthesis, i.e., before the formation of the oxetane ring. For this purpose, we favored an intramolecular Heck reaction (Scheme 18), clearly influenced by Overman's successes in the gelsemine area.[4h] To pave the way for this study, condensation of aldehyde **2** and HEW reagent **93** afforded the olefin. The latter underwent spontaneous divinylcyclopropane rearrangement to give iodoanilide **94**. Treatment of **94** with KO^{t}Bu afforded the conjugated isomer **95**. The latter was *N*-alkylated with MeI to provide **96**.

It was not clear that carbon−palladium bond formation would exhibit any preference for either the α- or β-face of **96**. However, by employing Overman's "ligandless" coupling conditions,[55] we expected that both C5−C16 and C3−C7 double bonds would coordinate with palladium in transition state **98**.

(53) Jahngen, E. G. E.; Rossomando, E. F. *Synth. Commun.* **1982**, *12*, 601−606.

(54) For additional examples of free radical reactions with isonitrile precursors to provide quinoline derivatives, see: Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194.

Scheme 18. Intramolecular Heck Reaction[a]



[a] Conditions and reagents: (a) LiCl, Hünig's base, CH_3CN, 60%; (b) KO^{t}Bu, HO^{t}Bu, 85 °C, 98%; (c) NaH, MeI, 70−80%; (d) 10% Pd_2dba_3·$CHCl_3$, 2 equiv of AgOTf, 20 equiv of Et_3N, 1,4-dioxane, 120 °C, 50−70%; (e) $Pd(PPh_3)_4$, CH_3CN; (f) $KO_2CN{=}NCO_2K$, MeOH/HOAc, 63%.

Accordingly, the carbon palladation would prefer to occur from the α-face of **96** to afford the desired oxindole **97a**. In the event, **96** was treated under the optimized conditions for this substrate, 10% of Pd_2dba_3·$CHCl_3$, 2 equiv of AgOTf, and 20 equiv of Et_3N in 1,4-dioxane at 120 °C in a sealed tube. These conditions led to a 7:1 mixture of **97a** and **97b**. By contrast, when **96** was treated with $Pd(PPh_3)_4$ in acetonitrile, there was obtained a 4:3 mixture of **97a** and **97b**. To further support this hypothesis, the C5−C16 double bond of **95** was selectively reduced with diimide to provide **99** and thence, following N-alkylation, **100**. Subjection of **100** to the same "ligandless" conditions afforded a 1:7 mixture of **101a** and **101b** favoring the carbon palladation from the *β*-face of **100**. The steric effect of sp^3 C5 and C16 in **100** may also be attributed to the change of facial selectivity. Unfortunately, the campaign to install the oxetane moiety starting from **97a** was not promising.

Completion of the Total Synthesis of (±)-Gelsemine. At this stage, compound **74** containing the six-membered spirolactam was our best hope for reaching gelsemine (**1**). To achieve the total synthesis goal, we faced the challenging prospect of contracting the six-membered lactam to the required five-membered spiroanilide.

The campaign to accomplish this final goal began with reduction of the imide-like functionality of **74**, thus affording aminal **102** (Scheme 19). In a key and little used type of step,[56] dehydration of this aminal linkage was accomplished, thereby furnishing enamide **103**. Dihydroxylation of **103**, across the more electron-rich enamide double bond, provided a trihydroxy intermediate, which was subjected to oxidative cleavage, as shown. *This degradation provided **104**, containing an all important β-face aldehyde at C7*. Protection of the hydroxy group of **104** led to silyl ether **105**. Treatment of this compound with K_2CO_3 in MeOH served to accomplish *N*-deformylation and, concurrently, ring closure to a cyclic hemi-aminal. The latter, following oxidation with reagent TPAP, gave rise to oxindole **106**.

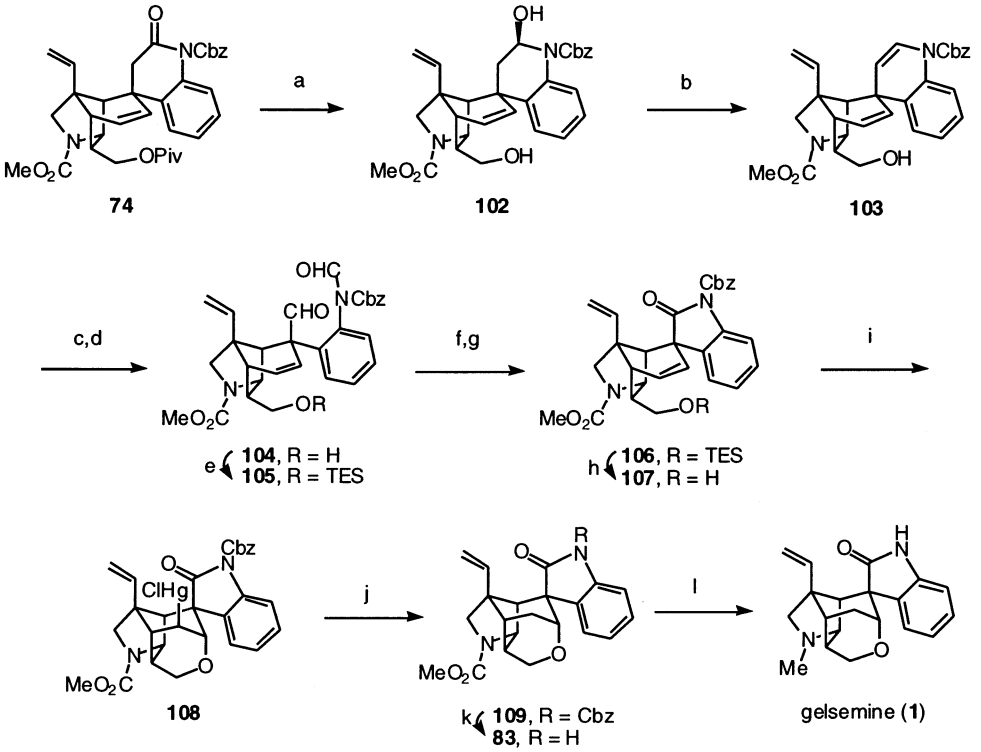
Desilylation of **106**, as shown, led to **107**, in which the extremely hindered free hydroxymethyl group on the α-face (initially derived by intramolecular oxetane opening) was now poised to close the tetrahydropyran ring. In the event, treatment of **107** with $Hg(OTf)_2$·*N*,*N*-dimethylaniline complex in CH_3NO_2[4a,f,g,57] afforded the desired mercuric cyclization product **108**. The mercuric intermediate, following reduction with $NaBH_4$ under basic conditions, indeed led to formation of a hydropyran ring as a mixture of free oxindole **83** and Cbz-protected oxindole **109**. This mixture was treated with 10% of NaOH in THF, thereby converging on **83** in 67% yield over two steps. In the final step of the synthesis, the methyl carbamate linkage of **83**

(55) (a) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785−3788. (b) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859−4862.

(56) For examples of the similar dehydration reactions using acids, see: (a) Nuti, V.; Saettone, M. F. *Tetrahedron* **1970**, *26*, 3875−3882. (b) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792−5796. (c) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586−7593.

(57) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806−813.

Scheme 19 [a]



[a] Conditions and reagents: (a) DIBAL, CH_2Cl_2, −78 °C, 86%; (b) $TsOH·H_2O$, CH_2Cl_2, reflux, 72%; (c) OsO_4, THF, −25 °C; $NaHSO_3$ (aqueous), 44% + 33% of starting material; (d) $NaIO_4$, THF/H_2O, 99%; (e) TESOTf, Et_3N, CH_2Cl_2, 0 °C, 52%; (f) K_2CO_3, MeOH; (g) TPAP, NMO, CH_2Cl_2, 4 Å MS, 78% for two steps; (h) HF·Py, THF, 0 °C, 99%; (i) $Hg(OTf)_2·C_6H_5NMe_2$, CH_3NO_2, 92%; (j) $NaBH_4$, 10% NaOH, EtOH/CH_2Cl_2; (k) 10% NaOH, THF, 67% over two steps; (l) $LiAlH_4$, THF, 0−25 °C, 81%.

was reduced to an *N*-methyl group with $LiAlH_4$.[58] In this way, (±)-gelsemine was isolated. Its spectroscopic and chromatographic properties matched those of naturally derived gelsemine.

Summary

Our orientation at the outset of the investigation was to use the total synthesis of gelsemine (**1**) as a launching point to explore some questions with potentially broader implications in organic chemistry. Indeed, all the key issues of selectivity, at both regiochemical and stereochemical levels, were resolved in favorable ways. Needless to say, confident predictions as to the applicability of these early findings to new cases should be tempered by caution, pending the broadening of our rather narrow data sets.

As for gelsemine itself, its total synthesis has been accomplished in a fashion reasonably related to our original prospectus. Obviously, the synthesis suffered from our inability to conduct the [2,3]-sigmatropic rearrangements on intermediates **51** and **54**. This setback necessitated a major remedial effort which, in the end, succeeded but not without serious compromise as regards conciseness. The problem of a fully satisfying total synthesis of gelsemine remains.

Acknowledgment. This work was supported by Grant HL25848 from the National Institutes of Health. H.L. thanks NIH Cancer Pharmacology Training Grant (T32-CA62948) for a postdoctoral fellowship and the Texaco Foundation for chemical support. We thank Dr. George Sukenick and Ms. Sylvi Rusli of the MSKCC NMR Core Facility for NMR and mass spectral analyses (NIH Grant CA08748). The receipt of a Pfizer Award to S.J.D. for Creative Work in Organic Synthesis is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **14**−**16**, **21**−**39**, **31**, **46**−**49**, **54**−**55**, **74**−**76**, **83**, and **102**−**109** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(58) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1985**, *52*, 79−83.

JA0204675