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Total Synthesis of (−)-Incarvilline, (+)-Incarvine C, and (−)-Incarvillateine

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Abstract: The first total syntheses of new monoterpene alkaloids (−)-incarvilline, (+)-incarvine C, and (−)-incarvillateine, corresponding to the natural enantiomers, have been accomplished. The strategy for the synthesis of these natural products utilized 6-*epi*-incarvilline as a common precursor, which was assembled by a three-component coupling reaction using (4*S*)-4-siloxy-2-cyclopenten-1-one to construct an appropriately trisubstituted cyclopentanone, followed by ring closure to the *cis*-perhydro-2-pyrindine skeleton by means of a reductive Heck-type reaction. Furthermore, topochemically controlled [2 + 2] photodimerization of cinnamic acid derivatives in the solid state for the stereospecific construction of a 1,2,3,4-tetrasubstituted cyclobutane ring was also investigated as a means to access (−)-incarvillateine.

Introduction

Incarvillateine (**1**) is a member of a new class of monoterpene alkaloids carrying a characteristic cyclobutane ring (Figure 1), first isolated from the aerial parts of *Incarvillea sinensis* Lam., which is a wild plant distributed in the northern area of China, that has been traditionally used in treating rheumatism and relieving pain as an ancient Chinese crude drug designated as "Jiaohao".[1] This compound has been found to show potent analgesic activity in a formalin-induced pain model in mice, and this action was in part blocked by naloxone, indicating a partial interaction with a central opioid mechanism.[2] In subsequent tests on mice, it was observed that the analgesic effect of **1** was significantly blocked by theophylline, an adenosine receptor antagonist, suggesting that the potent antinociceptive action of **1** is mainly mediated via an adenosine receptor mechanism rather than an opiate receptor mechanism.[3] Structure−activity relationship studies suggested that the cyclobutane moiety of **1** plays an important role in expression of antinociceptive action because incarvine C (**2**)[4] and incarvilline (**3**),[5] isolated from the same plant, and related compounds lacking the cyclobutane ring exhibited no or weak activity.[6]

The structures and relative stereochemistry of these compounds **1**−**3** (Figure 1), which share in common the monoterpene alkaloid moiety, were determined on the basis of spectroscopic data and X-ray crystallographic analysis.[1,5] The absolute configuration of incarvilline (**3**),[7] the core compound of these alkaloids **1**−**3**, has been assigned as shown based on Mosher's method and X-ray analysis of incarvilline methiodide. However, the absolute stereochemistry of incarvillateine (**1**) and incarvine C (**2**) has still not been established, although it is possible that the absolute stereochemistry of the monoterpene alkaloid moiety of these compounds is identical to that of incarvilline (**3**).

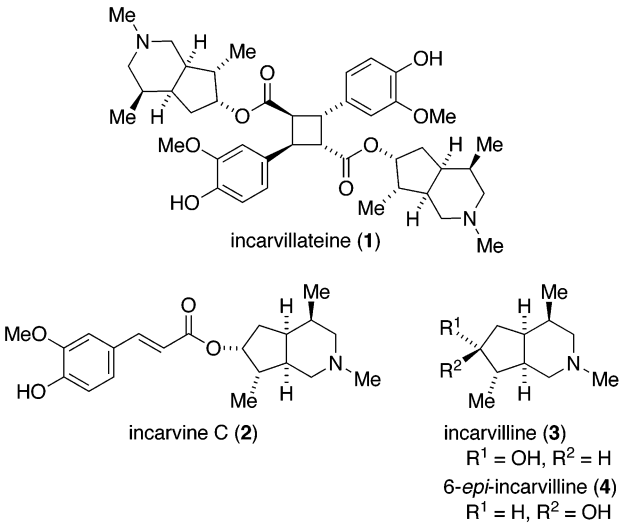
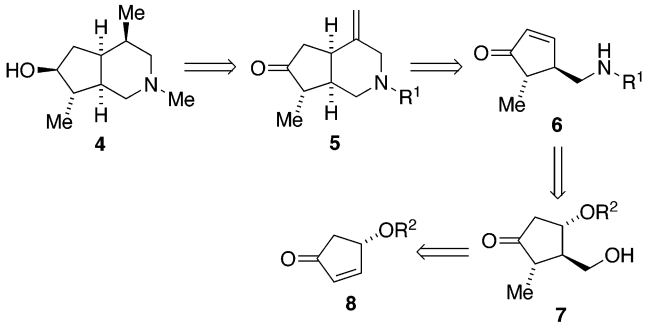


Figure 1. Structures of incarvillateine and related alkaloids.

The potential usefulness of **1** as a nonopioid analgesic agent and its unusual structural features have prompted us to initiate an effort directed toward its synthesis. In this paper, we describe

(1) Chi, Y.-M.; Yan, W.-M.; Li, J.-S. *Phytochemistry* **1990**, *29*, 2376−2378.
(2) Nakamura, M.; Chi, Y.-M.; Yan, W.-M.; Nakasugi, Y.; Yoshizawa, T.; Irino, N.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *J. Nat. Prod.* **1999**, *62*, 1293−1294.
(3) Chi, Y.-M.; Hashimoto, F.; Nohara, T.; Yan, W.-M.; Sakurada, S.; Nakamura, M.; Minagawa, Y.; Yoshizawa, T. *117th Annual Meeting of the Pharmaceutical Society of Japan*; Tokyo, March, 1997; Abstract 2, p 147.
(4) Chi, Y.-M.; Hashimoto, F.; Yan, W.-M.; Nohara, T. *Phytochemistry* **1995**, *39*, 1485−1487.
(5) Chi, Y.-M.; Yan, W.-M.; Chen, D.-C.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Phytochemistry* **1992**, *31*, 2930−2932.
(6) Nakamura, M.; Chi, Y.-M.; Yan, W.-M.; Yonezawa, A.; Nakasugi, Y.; Yoshizawa, T.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *Planta Med*. **2001**, *67*, 114−117.
(7) Chi, Y.-M.; Hashimoto, F.; Yan, W.-M.; Nohara, T.; Yamashita, M.; Marubayashi, N. *Chem. Pharm. Bull.* **1997**, *45*, 495−498.

Scheme 1



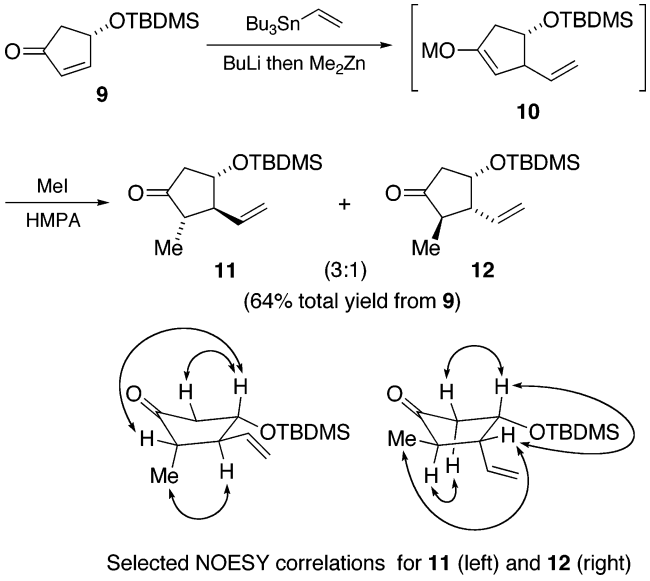
the first total synthesis of alkaloids **1**−**3** corresponding to the natural enantiomers, using 6-*epi*-incarvilline (**4**) as a common precursor. The strategy we have developed for assembling **4** involves the construction of an appropriately trisubstituted cyclopentanone via a three-component coupling reaction and then ring closure to the octahydrocyclopenta[*c*]pyridine (perhydro-2-pyridine) skeleton by means of a reductive Heck-type reaction. Furthermore, topochemically controlled [2 + 2] photodimerization of cinnamic acid derivatives in the solid state for the stereospecific construction of a 1,2,3,4-tetrasubstituted cyclobutane ring was also investigated as a means to access incarvillateine (**1**).

Results and Discussion

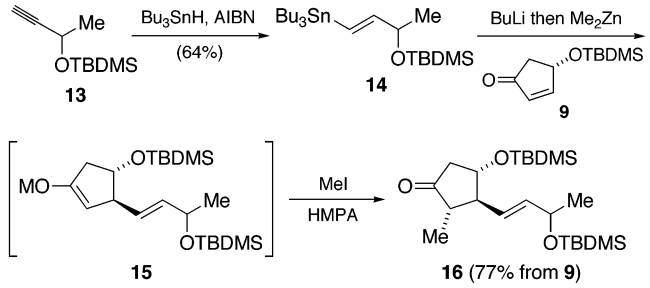
1. Synthesis of (−)-Incarvilline and (+)-Incarvine C. Our initial efforts on the synthesis of 6-*epi*-incarvilline (**4**) have focused on the preparation of the 2,3,4-trisubstituted cyclopentanone **7** with control of the relative and absolute configurations of the three contiguous stereocenters, as indicated in Scheme 1. We anticipated that stereocontrol elements and appropriate functionality for this purpose could be introduced via a three-component coupling reaction[8] using the cyclic enone **8**. To test the feasibility of this coupling protocol in an improved procedure using organozinc reagents,[9] we conducted preliminary experiments on the (*S*)-cyclopentenone **9**.[10] Thus, transmetalation of vinylstannane with BuLi into the lithium derivative followed by addition of Me_2Zn led to in situ generation of a vinyl zincate intermediate species that underwent conjugate addition to **9** (Scheme 2). The enolate **10** thus formed was quenched with iodomethane in the presence of HMPA to afford the adducts **11** and **12** in 64% combined yield as a diastereomeric mixture favoring the all-trans isomer **11** with the desired configuration at C3, but suffering from low diastereoselectivity (3:1). The stereochemistries of these products **11** and **12** were assigned on the basis of NOESY spectral data (Scheme 2).

From these results, we anticipated that the all-trans diastereoselectivity could be enhanced by increasing the steric bulk around the olefin of the zincate intermediate in the conjugate addition to the enone. Indeed, when the (*E*)-alkenyl zincate intermediate generated in situ by transmetalation of (*E*)-alkenylstannane **14**, prepared by hydrostannylation of the alkyne **13**, was allowed to react with (*S*)-enone **9**, followed by quenching with iodomethane in a manner similar to that described above for the preparation of **11** and **12**, the three-component coupling product **16** was formed in 77% yield from **9** (Scheme 3). Although **16** was an inseparable 1:1 mixture of diastereomers epimeric at the stereogenic center bearing the siloxy group on the olefinic side chain, the reaction proceeded with complete all-trans stereoselection with respect to the stereocenters of the cyclopentane ring.

Scheme 2



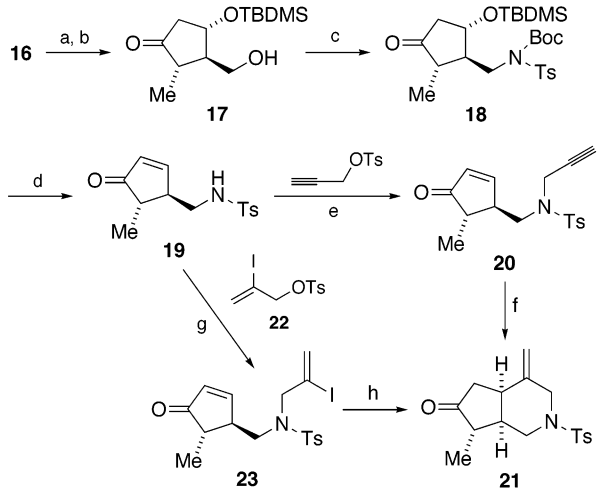
Scheme 3



The 2,3,4-trisubstituted cyclopentane **16** thus obtained was subjected to ozonolysis followed by borohydride reduction of the intermediate aldehyde to give the alcohol **17** (68% yield), which underwent Mitsunobu reaction with *N*-Boc-tosyl amide to afford the tosylated amide **18** (99% yield) (Scheme 4). Upon exposure of **18** to trifluoroacetic acid (CH_2Cl_2, room temperature), deprotection of the Boc group and elimination of the siloxy group[11] occurred in one operation to produce the enone **19** in excellent yield (95%). For the construction of the perhydro-2-pyridine core,[12] we envisioned a strategy based on palladium-catalyzed enyne bicyclization[13] which has been applied by us

(8) For a review on "three-component coupling", see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847−876.
(9) Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799−11805.
(10) Compound **9** was prepared via TBDMS protection (Tanaka, T.; Kurozumi, S.; Toru, T.; Miura, S.; Kobayashi, M.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1713−1718) of 4(*S*)-hydroxycyclopent-2-enone. For the preparation of the latter compound, see: (a) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1976**, 759−762. (b) Khanapure, S. P.; Najafi, N.; Manna, S.; Yang, J.-J.; Rokach, J. *J. Org. Chem.* **1995**, *60*, 7548−7551.
(11) This process involving elimination of the siloxy group seems unusual because there are some cases on trifluoroacetic acid-mediated Boc removal without concomitant loss of a silyl protecting group from an alcohol. As suggested by a referee, the elimination process in this case may be explained by a mechanism via an enol intermediate.
(12) For the construction of the 2-pyrindine ring system, see: (a) Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409−1417. (b) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2003**, *5*, 1689−1692.
(13) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34−42.

Scheme 4 [a]

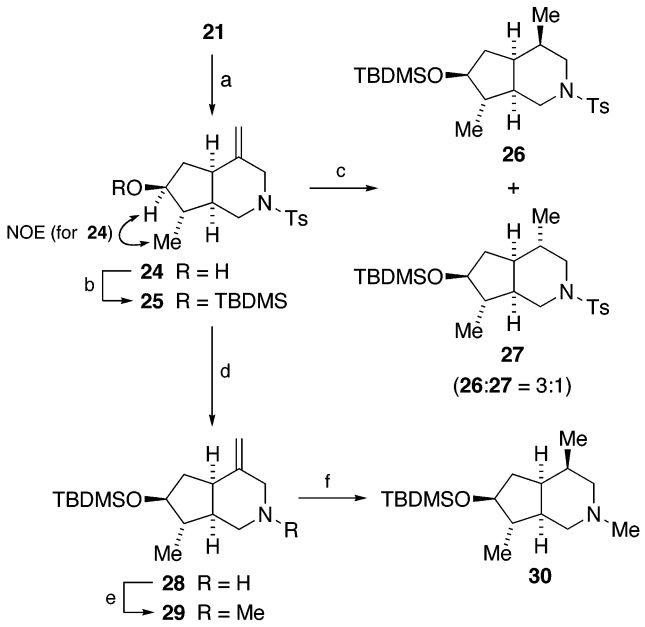


[a] Reagents and conditions: (a) O_3, CH_2Cl_2−MeOH, −78 °C, then Me_2S, 96%; (b) $NaBH_4$, EtOH, 0 °C, 71%; (c) TsNHBoc, DEAD, Ph_3P, THF, room temperature, 99%; (d) CF_3CO_2H, CH_2Cl_2, room temperature, 95%; (e) K_2CO_3, CH_3CN, reflux, 81%; (f) $Pd(OAc)_2$, BBEDA, PMHS, benzene, 95 °C, 9%; (g) K_2CO_3, CH_3CN, reflux, 80%; (h) $PdCl_2(CH_3CN)_2$, Et_3N, HCO_2H, CH_3CN, room temperature, 72%.

to the construction of the 1-pyrindine skeleton in the total synthesis of streptazolin.[14] Thus, the *N*-tosyl amide **19** was propargylated using the tosylate of propargyl alcohol under basic conditions to give the enyne compound **20**. Upon treatment of **20** with 10 mol % of $Pd(OAc)_2$ and *N*,*N*′-bis(benzylidene)-ethylenediamine (BBEDA) in the presence of polymethylhydrosiloxane (PMHS), reductive cyclization proceeded to give the expected *cis*-perhydro-2-pyrindine **21**; however, the poor yield (9%) rendered this transformation of little value (Scheme 4). Thus, we sought to develop an alternative palladium-mediated cyclization methodology for the synthesis of **21**. In this regard, our attention next was focused on a reductive Heck-type reaction which has been employed for palladium-catalyzed conjugate addition of aryl iodides.[15] To apply this method to intramolecular vinylation, the *N*-tosyl amide **19** was converted to the alkenyl iodide **23** by treatment with 2-iodo-2-propenyl tosylate (**22**) and K_2CO_3. Upon treatment of **23** with $PdCl_2(CH_3CN)_2$ in the presence of triethylamine and formic acid, a reductive cyclization proceeded with exclusive formation of **21** in 72% yield. The *cis*-stereochemistry of the ring fusion in **21** was confirmed by a NOESY interaction observed between the two angular hydrogens.

Reduction of **21** with sodium borohydride provided the (6*S*)-alcohol **24** as a single isomer in 97% yield (Scheme 5). The stereochemistry of the hydroxyl group of **24** was confirmed by NOE analysis. After protection of the secondary alcohol as its TBDMS ether, compound **25** was subjected to catalytic hydrogenation over PtO_2 in MeOH, resulting in the β-methyl product **26** and its epimer **27** as a 3:1 diastereomeric mixture. The observed 3:1 preference for the formation of **26** with the desired stereochemistry at C4 can be understood as arising from hydrogenation of **25** on the convex face of the *cis*-fused ring system. When the hydrogenation was carried out (PtO_2, 5 atm, MeOH) using **29** with a methyl group on nitrogen instead of the tosyl group as in **25**, complete diastereoselectivity was realized for the formation of **30** (84% yield) with the desired 4*R* configuration.

Scheme 5 [a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 97%; (b) TBDMSCl, imidazole, 93%; (c) H_2, PtO_2, MeOH, 96%; (d) sodium naphthalenide, DME, −50 °C, 78%; (e) 35% HCHO, $NaBH_3CN$, AcOH, CH_3CN, 97%; (f) H_2, PtO_2, 5 atm, MeOH, 84%.

Deprotection of the TBDMS group in **30** with Bu_4NF furnished (+)-6-*epi*-incarvilline (**4**) [$[\alpha]^{20}_D$ +18.1 (*c* 1.42, ($CHCl_3$)]. Inversion of configuration of the C6 hydroxyl stereocenter was accomplished using Mitsunobu reaction with *p*-nitrobenzoic acid[16] followed by hydrolysis of the resulting epimeric *p*-nitrobenzoate **31**, leading to the synthesis of (−)-incarvilline (**3**) as a white crystalline solid: mp 94.4−95.5 °C (lit.[5] mp 93.4−93.8 °C); $[\alpha]^{20}_D$ −8.1 (*c* 0.18, $CHCl_3$) [lit.[5] $[\alpha]^{24}_D$ −8.0 (*c* 1.24, $CHCl_3$)], exhibited ^1H and ^{13}C NMR data identical to those reported[5] for the natural product (Scheme 6).

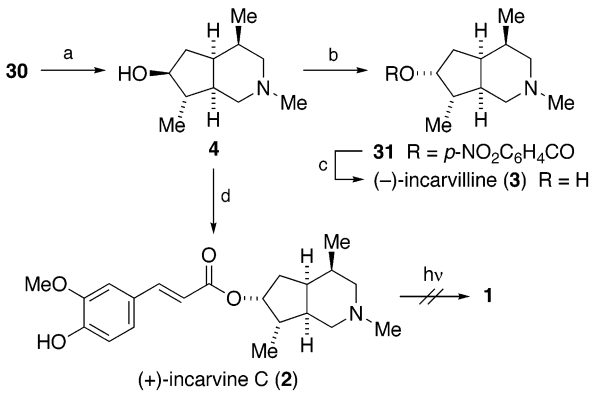
On the other hand, **4** underwent Mitsunobu condensation with (*E*)-ferulic acid (4-hydroxy-3-methoxycinnamic acid) (**32**) with complete inversion of configuration at C6, furnishing (+)-incarvine C (**2**) whose spectral properties (^1H and ^{13}C NMR) were identical to those published[4] for natural incarvine C (Scheme 6). We were surprised to find, however, that the optical rotation of the synthetic material [$[\alpha]^{20}_D$ +20.0 (*c* 0.46, $CHCl_3$)] was almost equal in magnitude but opposite in sign to that [$[\alpha]_D$ −20.8 (*c* 0.46, $CHCl_3$)] published[4] for the natural product. This lack of congruence indicated that the synthetic dextrorotatory incarvine C (**2**), which possesses the same absolute configuration as natural incarvilline (**3**) at all stereogenic centers, is the unnatural enantiomer, despite the fact that incarvine C is considered to be biogenetically derived from incarvilline. We therefore undertook a study to verify the absolute configuration of natural incarvine C by HPLC analysis on a chiral phase [Daisel Chiralcel OD 0.46 × 25 cm; eluent, hexane/EtOH/Et_2NH (38:2:1); flow rate, 0.5 mL/min; UV detection, 254 nm].

(14) (a) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054−1059. (b) Yamada, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *48*, 8787−8790.

(15) (a) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236−4240. (b) Schmidt, B.; Hoffmann, H. M. R. *Tetrahedron* **1991**, *47*, 9357−9368.

(16) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020. (b) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234−236.

Scheme 6 [a]



[a] Reagents and conditions: (a) Bu_4NF, THF, room temperature, 97%; (b) *p*-$NO_2C_6H_4CO_2H$, DEAD, Ph_3P, THF, room temperature, 66%; (c) NaOH, THF, 67%; (d) (*E*)-ferulic acid (**32**), DEAD, Ph_3P, THF, room temperature, 6 d, 36% (51% based on recovery of the starting material).

Racemic incarvine C (*rac*-**2**), prepared starting with the known[17] racemic enone *rac*-**9** by the same reaction sequence used for the synthesis of (+)-incarvine C (**2**), gave two well-separated peaks for the two enantiomers at retention times of 47 and 51 min. The synthetic sample of (+)-incarvine C (**2**) revealed a peak at longer retention time (51 min) and was found to have the retention time identical to that of the natural product. All of these results revealed that the synthetic (+)-incarvine C (**2**) corresponds to the natural enantiomer, thus allowing the absolute configuration of the natural product to be assigned as structure **2**, and confirmed our suspicion that the original optical rotation value (−20.8)[4] for natural incarvine C is erroneous.

To complete the synthesis of incarvillateine (**1**), we attempted to dimerize **2** under UV irradiation in the solid state; however, this approach led mostly to decomposition giving an intractable mixture.

2. Photodimerization of the Ferulic Acid Derivatives. To circumvent the problem associated with the dimerization of **2**, we turned to solid-state photodimerization using crystalline derivatives of ferulic acid (**32**), which we anticipated would lead to stereospecific construction of the α-truxillic acid derivatives featuring a 1,2,3,4-tetrasubstituted cyclobutane ring with the desired stereochemistry of incarvillateine (**1**).

The [2 + 2] photodimerization of *trans*-cinnamic acids in the crystalline state has been extensively investigated by Schmidt and co-workers.[18] They have demonstrated that such reactions are strictly controlled by the packing arrangement of molecules. The cinnamic acids are observed to crystallize in three polymorphic forms, α, *β*, and *γ*, and on photolysis of the crystal, while in solution trans−cis isomerization occurs, and the formation of α-truxillic and *β*-truxinic acids proceeds via the α- and *β*-crystalline forms in which the cinnamic acid molecules are stacked in anti head-to-tail and syn head-to-head conformations, respectively (Figure 2). The *γ*-modification in which the cinnamic acid is also packed head-to-head, but the molecules do not overlap and, furthermore, the distance between them is large (4.7−5.1 Å), is unreactive. Based on these studies on the cinnamic acids, it was empirically deduced that the olefins

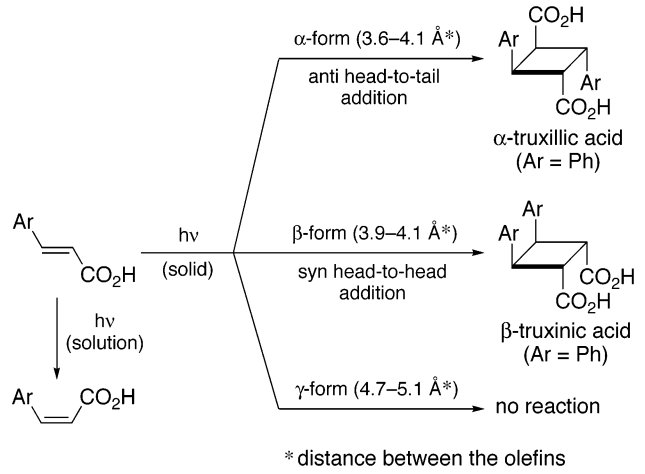
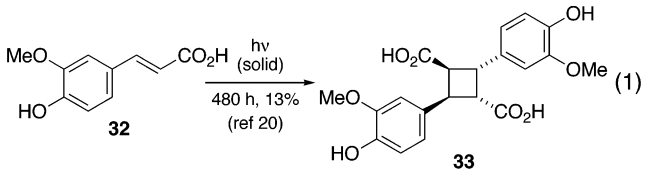


Figure 2. Topochemical [2 + 2] photodimerization of cinnamic acids.

should lie in parallel planes with the double bonds oriented in the same direction with the distance between the olefins of less than 4.2 Å for dimerization to occur.

These "topochemical rules", thus developed, can be used to predict the reactivity and stereoselectivity in crystal lattice-controlled photocycloadditions; however, the difficulty in forming the desired type of crystalline structure in any given case is a major problem in applying these rules, for the factors that control crystal packing are not yet well understood. This facet of organic solid-state chemistry has been referred to as crystal engineering and has been actively pursued in recent years.[19] In the case of ferulic acid (**32**), it has been shown that on photolysis of crystalline **32** the rate of dimerization was very slow (requiring 480 h for 50% conversion) and the yield of 4,4′-dihydroxy-3,3′-diemthoxy-α-truxillic acid (**33**) was very poor (13%) (eq 1),[20] probably due to the monomers being too far apart in the crystal lattice.

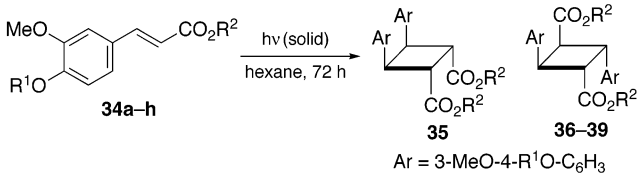


We thus decided to focus our efforts on the development of a practical and efficient synthesis of derivatives of **33** by topochemical solid-state photodimerization. Summarized in Table 1 are the results for photodimerization of the ferulic acid derivatives **34a**−**h** which were simply prepared from commercially available ferulic acid (**32**) as crystalline products. In all cases, the powdered crystalline materials were suspended in hexane[21] and subjected to irradiation through Pyrex for 72 h.

Exposure of *p*-nitrophenyl ferulate (**34a**) to these conditions afforded the photodimer **35** in 63% yield (entry 1); however, its syn head-to-head *β*-truxinic stereochemistry assigned by X-ray analysis (Figure 3) is not consistent with the stereostructure of the cyclobutane moiety of incarvillateine (**1**). The 4-*O*-

(17) For the preparation of *rac*-**9**, see: Hamann, P. R.; Wissner, A. *Synth. Commun.* **1989**, *19*, 1509−1518.
(18) (a) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996−2000. (b) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 2000−2013. (c) Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 2014−2021.
(19) For reviews on photodimerization in the solid state, see: (a) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647−678. (b) Thomas, J. M. *Pure Appl. Chem.* **1979**, *51*, 1065−1082. (c) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433−481.
(20) Morrison, W. H., III; Hartley, R. D.; Himmelsbach, D. S. *J. Agric. Food Chem.* **1992**, *40*, 768−771.
(21) When the photoreaction was carried out by irradiating aqueous suspensions of the ferulate derivatives **34**, the esters were found to be partly hydrolyzed.

Table 1. Photodimerization of the Ferulic Acid Derivatives **34a**−**h**



entry	compound	R^1	R^2	photodimer	yield (%)
1	**34a**	H	*p*-NO_2Ph	**35**	63
2	**34b**	Ac	Me	na[a]	
3	**34c**	PhCO	Me	na	
4	**34d**	Ms	Me	**36**	35
5	**34e**	$PhSO_2$	Me	na	
6	**34f**	*o*-Ns[b]	Me	**37**	56
7	**34g**	Ts	Me	**38**	60
8	**34h**	Ts	H	**39**	98

[a] na = not available. [b] *o*-Ns = *o*-$NO_2C_6H_4SO_2$.

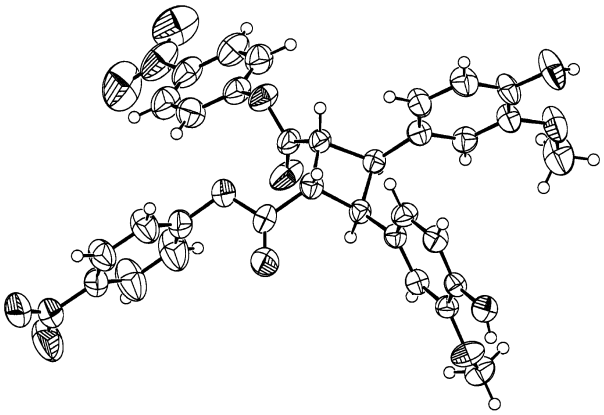


Figure 3. ORTEP drawing of the X-ray crystal structure of **35**.

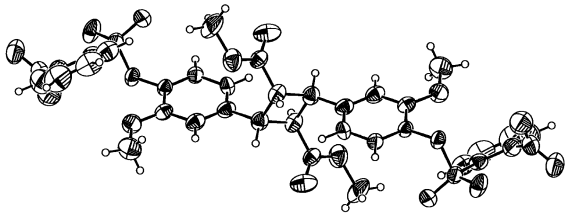


Figure 4. ORTEP drawing of the X-ray crystal structure of **37**.

acetyl and 4-*O*-benzoyl derivatives of methyl ferulate, **34b** and **34c**, produced no dimeric materials (entries 2 and 3), but the 4-*O*-mesyl derivative **34d** did afford the desired α-truxillic head-to-tail dimer **36**, albeit in low yield (entry 4). On the basis of this result, we considered the possibility that a 4-*O*-sulfonyl group in methyl ferulate may play a significant role in achieving an appropriate packing arrangement for α-dimerization to occur. Of the three 4-*O*-sulfonyl derivatives **34e**−**g** thus prepared, no dimerization was observed for the benzenesulfonyl derivative **34e**, but the *o*-nitrosyl and tosyl derivatives, **34f** and **34g**, respectively, indeed underwent topochemically controlled α-dimerization to form the corresponding head-to-tail adducts **37** and **38** in moderate yields (entries 6 and 7). The stereochemistries of **37** and **38** are secured by X-ray analyses (Figures 4 and 5). Quite remarkably, when 4-*O*-tosylferulic acid (**34h**) was used (entry 8), the α-truxillic adduct **39** was found to be formed in excellent yield (98%). The structure of **39** was confirmed by conversion to the corresponding methyl ester **38**.

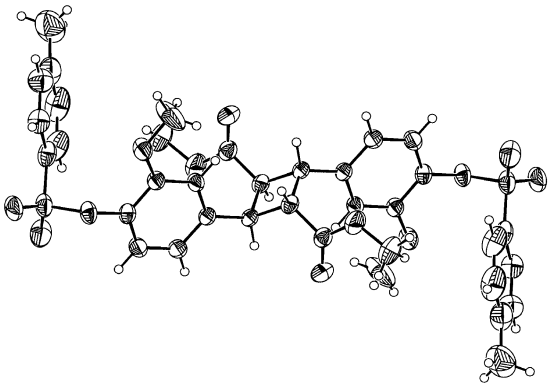


Figure 5. ORTEP drawing of the X-ray crystal structure of **38**.

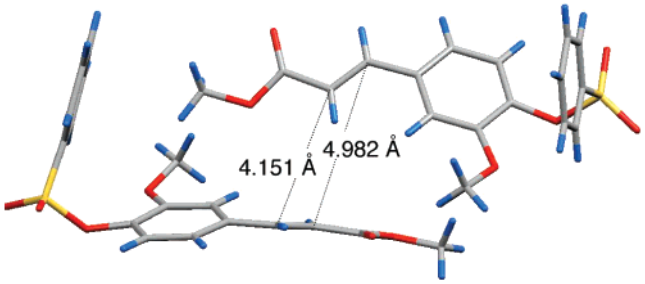


Figure 6. Unit cell packing arrangent of **34e**.

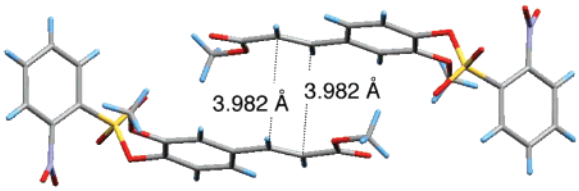


Figure 7. Unit cell packing arrangement of **34f**.

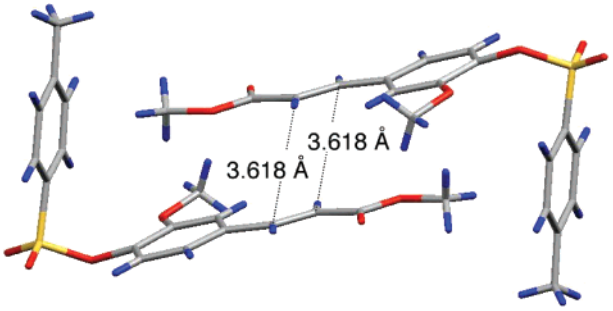
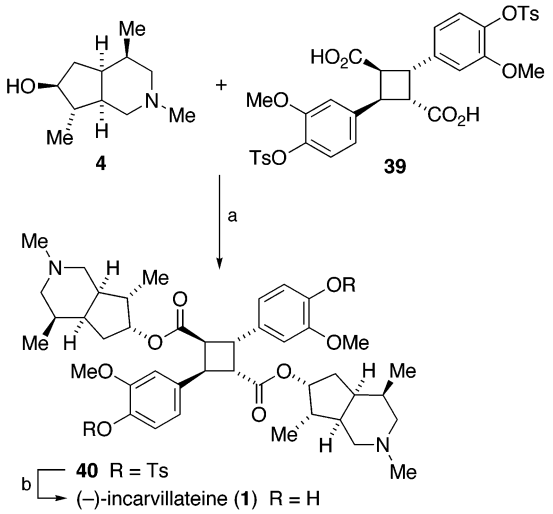


Figure 8. Unit cell packing arrangement of **34g**.

The photobehaviors of these 4-*O*-sulfonyl derivatives of ferulate, **34e**−**g**, can be rationalized by their packing arrangements in the crystal structures. In the case of the benzenesulfonate **34e** (Figure 6), two molecules included in a unit cell are not parallel and intermolecular adjacent double bonds are inclined to each other with distances of 4.15 and 4.98 Å, and so photodimerization does not occur. In the cases of the *o*-nitrosylate **34f** (Figure 7) and the tosylate **34g** (Figure 8), the parallel monomer molecules are arranged in the α-type packing mode with interdouble bond distances of 3.98 and 3.62 Å, respectively, and react to yield the expected photodimers **37** and **38** as single isomers. The excellent yield for the formation of the α-truxillic acid **39** suggests that 4-*O*-tosylferulic acid **34h** packs in a potentially reactive crystal structure (short parallel contact) in the α-type.

Scheme 7 [a]



[a] Reagents and conditions: (a) DEAD, Ph_3P, THF, 90 °C, 40%; (b) Na(Hg), MeOH, room temperature, 58%.

3. Total Synthesis of (−)-Incarvillateine. Having established a highly efficient method for the preparation of the α-truxillic head-to-tail photodimer, we turned our attention to the remaining steps necessary to complete the synthesis of incarvillateine (**1**). Thus, condensation of the α-truxillic acid **39** with 2 equiv of the above-described (+)-6-*epi*-incarvilline (**4**) under Mitsunobu conditions produced tosyl-protected incarvillateine (**40**) (Scheme 7). Finally, deprotection of the tosyl groups using sodium amalgam in methanol provided (−)-incarvillateine (**1**) as colorless crystals: mp 217−218 °C (lit.[22] mp 217.2−217.7 °C). The optical rotation $[\alpha]^{20}_D$ −10.9 (*c* 0.06, $CHCl_3$) [lit.[22] $[\alpha]_D$ −10.8 (*c* 0.79, $CHCl_3$)] and spectroscopic properties (^1H and ^{13}C NMR) of synthetic **1** were in agreement with those reported[23] for natural incarvillateine. The completion of the first synthesis of incarvillateine firmly establishes the structure and absolute stereochemistry of this interesting antinociceptive monoterpene alkaloid as **1**.

Conclusion

The first total syntheses of new monoterpene alkaloids (−)-incarvillateine (**1**), (+)-incarvine C (**2**), and (−)-incarvilline (**3**), corresponding to the natural enantiomers, was accomplished, using (+)-6-*epi*-incarvilline (**4**) as a common precursor, which allowed us to establish their structures and absolute configurations. The strategy we have developed for assembling **4** involves the stereoselective construction of an appropriately trisubstituted cyclopentanone via a three-component coupling reaction and ring closure to the *cis*-perhydro-2-pyrindine skeleton by means of a reductive Heck-type reaction. Furthermore, topochemically controlled [2 + 2] photodimerization of cinnamic acid derivatives in the solid state for the stereospecific construction of a 1,2,3,4-tetrasubstituted cyclobutane ring was also investigated as a means to access (−)-incarvillateine (**1**).

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Supporting Information Available: Experimental procedures and spectral data for new compound (PDF); X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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