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Synthetic studies on the erythrina alkaloids. Preparation of (±)-2-*epi*-erythrinitol

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Abstract

The erythrina alkaloid, 1,3,4,6-tetrahydro-3,15,16-trimethoxyerythrinan-2-ol (2-*epi*-erythrinitol), has been synthesized by a sequence featuring a [1+4] vinyl isocyanate–isocyanide cycloaddition followed by an intramolecular Heck reaction for assembly of the erythrinan ring system. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: alkaloids; Heck reaction; isocyanates.

The erythrinan alkaloid[1,2] 1,3,4,6-tetrahydro-3,15,16-trimethoxyerythrinan-2-ol (also know as 'erythritol' or 'erythrinitol') (**1**) was isolated from the methanol extract of *Erythrina variegata* flowers several years ago by Chawla and Sharma.[3] While the gross structure of this natural product has been established by spectral means, the stereochemical features of the compound remain uncertain. This material presents some interesting preparative challenges, and the stereochemical consequences of our recently disclosed Heck cyclization protocol for entry into the erythrinan skeleton could be employed to advantage for shedding some additional light on the details of its stereo-structure.[4] The construction of this alkaloid, as initially envisioned, would feature a [1+4] vinyl isocyanate–isocyanide cycloaddition for assembling an appropriately functionalized hydroindolone species upon which the remaining elements of the erythrinan system could be elaborated. This latter objective would be accomplished by applying our Heck cyclization protocol for introducing rings C and D of the target tetracycle. In this instance the *syn*-nature of the β-H elimination step of the Heck insertion process (**3**→**2**) (Scheme 1) would result in an obligatory *cis*-relationship between the incipient stereogenic center at C5 and the protected hydroxyl function at C2. The retrosynthesis plan for production of the unnatural epimer of this alkaloid, 2-*epi*-erythrinitol, is depicted in Scheme 1.

The synthesis commenced with a smooth [1+4] cycloaddition between the readily available, substituted vinyl isocyanate **4**[4] and cyclohexyl isocyanide, which serves as a 1,1-dipole equivalent,[5] to afford the hydroindolone building block **5**[6] in 70% yield (Scheme 2). Routine installation of the tethered iodoarene

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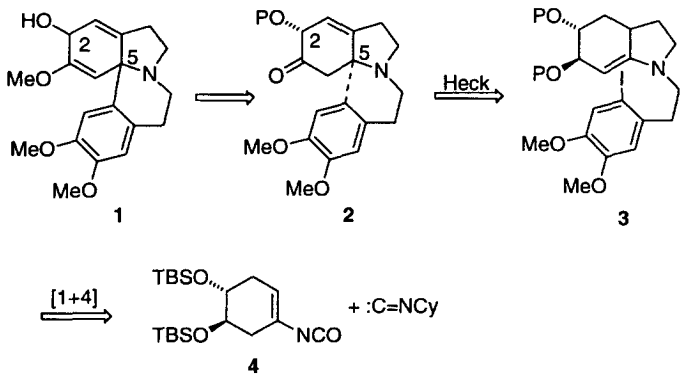
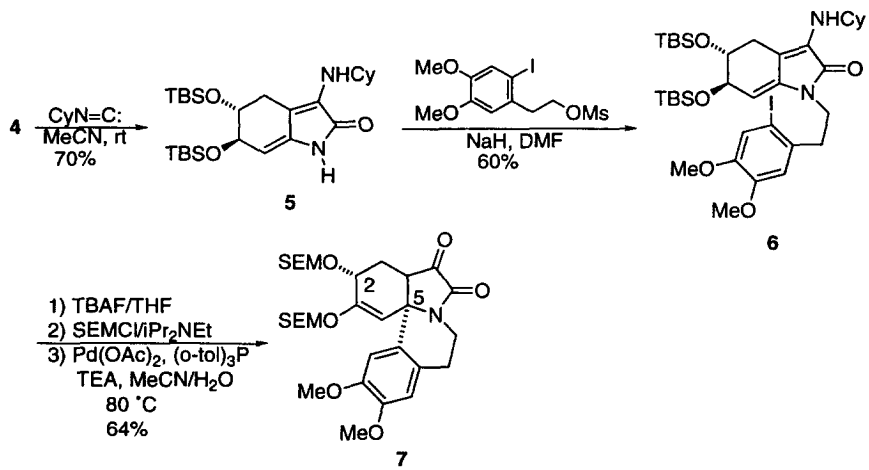


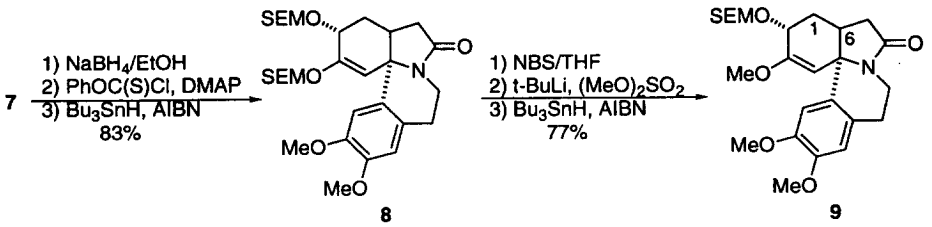
Scheme 1.

moiety followed to deliver **6**[6] in good yield, thus setting the stage for the critical Pd-mediated arylation step. Efforts to cyclize this material under a variety of Heck conditions met with little success, a consequence, it was assumed, of the steric bulk of the TBS groups. In response to this notion, the TBS protection was replaced with less-hindered SEM ether groups, and to our delight, the Pd-mediated cyclization now proceeded effectively to afford erythrinan **7**[6] as a single diastereomer, after hydrolysis of the labile enamine function. As noted earlier, the stereochemical requirements of the Heck process dictate the formation of a product in which the silyl ether located at C2 in compound **7** and the newly installed aryl substituent at C5 must be *cis* to each other. This outcome stems directly from the *trans* relationship that exists between the vicinal silyloxy substituents in the cyclization substrate.[7]



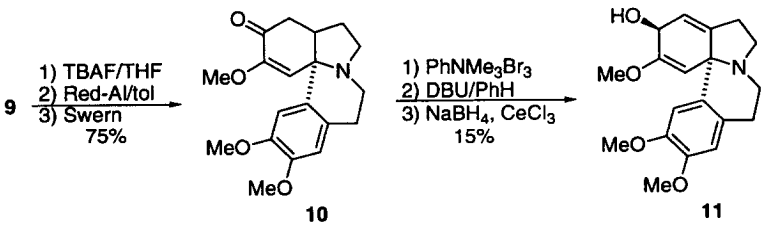
Scheme 2.

With the full erythrinan skeleton now in hand, attention turned to A-ring functional group processing. Thus, compound **7** was deoxygenated in straightforward fashion using the Barton–McCombie protocol[8] in high overall yield to give **8**,[6] which was then converted by an interesting series of steps into the methyl enol ether function ultimately required in the target. Thus, exposure of **8** to NBS gave the corresponding α-bromoketone in virtually quantitative yield. This material was then treated with *t*-BuLi/$(MeO)_2SO_2$ followed by reductive debromination with *n*-Bu_3SnH to afford compound **9**[6] in 77% overall yield for the three steps (Eq. 1).



(1)

At this juncture in the synthesis, considerable effort was expended in an attempt to introduce the remaining $\Delta^{1,6}$-alkene into compound **9** through manipulation of the lactam unit. Unfortunately, while the $\Delta^{6,7}$-unsaturation was easily accessed, translocation to the requisite deconjugated position proved to be particularly difficult, and it was finally abandoned. In the end, this objective could only be achieved through a sequence of steps that involved oxidation of the C2 hydroxyl group to the corresponding ketone so that direct introduction of the alkene could be implemented. We were, of course, cognizant of the fact that this operation would sacrifice the relative stereochemistry established during the Heck cyclization, however, no other options that would avoid this development presented themselves at the time. In the event, the SEM group was routinely removed, the lactam was cleanly reduced with Red-Al, and the free C2 alcohol oxidized to give ketone **10**[6] (mp 171–172°C).



(2)

The synthesis end-game was then reduced to a straightforward introduction of the $\Delta^{1,6}$-unsaturation followed by reduction of the carbonyl group at C2 in a stereocontrolled fashion. Toward this end, compound **10** was treated with $PhNMe_3Br_3$ in THF at 0°C to afford the corresponding α-bromoketone which was exposed to DBU in hot benzene and then reduced under standard Luche conditions to give erythrinan **11**[6] (mp 166–167°C) as a *single* diastereomer, the structure of which was confirmed by single crystal X-ray analysis. It is noteworthy that compound **11** is epimeric at C2 relative to earlier intermediates in this synthesis, and efforts to invert this center were not fruitful. While the ^1H and ^{13}C NMR data of compound **11** were to a large extent similar to those reported for the natural product, they were not identical, with the largest discrepancies occurring between sets of signals attributable to the protons and carbons in the vicinity of the putative epimeric alcohol centers. Thus, it can be concluded with some confidence that the natural substance is epimeric to compound **11** at C2.[9]

Acknowledgements

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6. This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR, MS) and analytical (combustion analysis and/or HRMS) data in complete accord with the assigned structure.
7. Unfortunately, efforts to install the SEM protection earlier in the synthetic sequence proved to be problematic.
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9. Efforts to obtain an authentic sample of the natural product for purposes of comparison with our synthetic material were unsuccessful. Therefore, strictly speaking, one cannot exclude the possibility that natural erythrinitol, in fact, possesses a structure that is different from the one reported in the original paper.