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Efficient Synthesis of Pyrrolizidine and Indolizidine Derivatives Using Nickel-Catalyzed Cyclization of 1,3-Diene and Aldehyde: Formal Total Synthesis of (-)-Elaeokanine C

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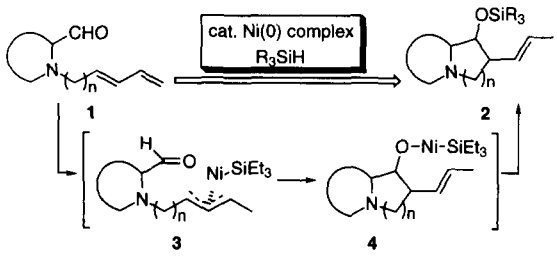
Abstract: Pyrrolizidine and indolizidine skeletons were successfully constructed by nickel-catalyzed cyclization of 1,3-diene and aldehyde in a chain. A formal total synthesis of an Elaeocarpus alkaloid, (-)-Elaeokanine C, in the naturally occurring form was achieved using this cyclization. © 1997 Elsevier Science Ltd.

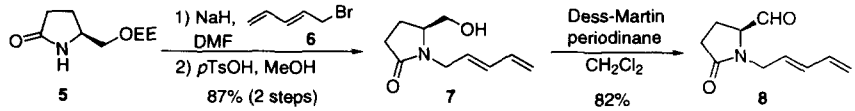
Construction of pyrrolizidine and indolizidine skeletons is very important for the synthesis of naturally occurring substrates and biologically active substances.[1] Recently, we reported a novel nickel-promoted stereoselective cyclization of 1,3-diene and a carbonyl group *via* a π-allylnickel intermediate.[2] The versatility of this cyclization encouraged us to apply this approach to the synthesis of these skeletons. Our plan is shown in Scheme 1. Reaction of 1,3-diene **1** with a hydride nickel complex, generated by the oxidative addition of R_3SiH to a zerovalent nickel complex, would give π-allylnickel complex **3**, which would react with the aldehyde moiety in the side chain to give complex **4**. Reductive elimination would then occur to give nitrogen-containing bicyclic compound **2** stereoselectively.

Scheme 1



To examine the feasibility of the above plan, the cyclization of **8** was attempted. The starting diene **8** was easily prepared in an optically active form (>99% ee)[3] by the coupling reaction of (*S*)-pyroglutamic acid derivative **5**[4] with **6**[5] followed by deprotection of the ethoxyethyl group and oxidation with Dess-Martin reagent.[6]

Scheme 2



Treatment of **8** with 20 mol % $Ni(cod)_2$ and 40 mol % PPh_3 in the presence of Et_3SiH in degassed toluene at room temperature for 13.5 hr provided indolizidine derivatives **9a** and **10a** in yields of 49% and 15%, respectively (Table 1, run 1).[7]

The enantiomeric excesses of **9a** and **10a** were determined to be 97% ee and 96% ee by HPLC analysis, which indicated that the optical purity of the starting material **8** was completely retained during cyclization. Although various solvents were investigated in the cyclization of **8** using Et_3SiH as a hydride source, the ratio of **9a** to **10a** was not improved. On the other hand, we were very surprised to know that the use of Ph_3SiH as a hydride source accelerated the reaction rate and improved the ratio of **9** to **10**. The cyclization of **8** with 20 mol % $Ni(cod)_2$ and 40 mol % PPh_3 in the presence of Ph_3SiH in THF was completed within 1 hr at room temperature to give **9b** in 68% yield (93% ee) and **10b** in 9% yield (97% ee). Furthermore, the cyclization of **8** at 0 °C gave **9b** in 73% yield (97% ee) and **10b** in 8% yield (99% ee). These results indicate that the formation of **9b**, which has both a triphenylsilyloxy group and a 1-propenyl group on the convex face of a 5-5 bicyclic framework, is preferable to that of **10b**, in which both groups are on the concave face.

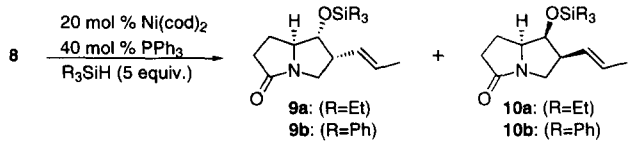


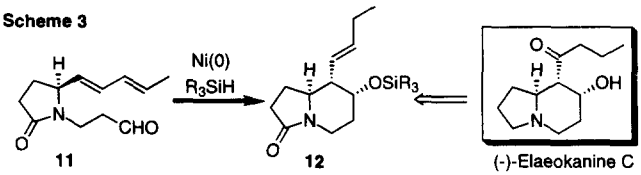
Table 1. Cyclization of **8** under the various conditions

run	solvent	R_3SiH	temp	time (hr)	yield (%) (9+10)	ratio (9/10)	ee (%)[a] (9/10)
1	toluene	Et_3SiH	rt	13.5	64	3.3/1	97/96
2	THF	Et_3SiH	rt	12.5	75	4.4/1	97/95
3	DMF	Et_3SiH	rt	13	75	3.7/1	97/94
4	CH_3CN	Et_3SiH	rt	94	30	6.5/1	95/93
5	THF	Ph_3SiH	rt	1	77	7.6/1	93/97
6	THF	Ph_3SiH	0 °C	1.5	81	9.1/1	97/99

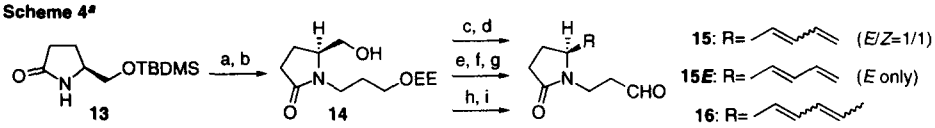
[a] The ee of **9** or **10** was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane/ ^{i}PrOH=9/1) of the corresponding benzoate, respectively.

Having established the construction of a pyrrolizidine skeleton using nickel-catalyzed cyclization, we turned our attention to the synthesis of a natural product. If the cyclization of **11**, which has a substituent on the 1,3-diene moiety, proceeds in a manner similar to the synthesis of the pyrrolizidine skeleton, we should obtain the indolizidine derivative **12**, which could be easily converted into the Elaeocarpus alkaloid, (-)-Elaeokanine C.[8,9] The substrates were synthesized as shown in Scheme 4.

Scheme 3



Scheme 4[a]



[a] (a) NaH, $Br(CH_2)_3OEE$ (**17**), 89%. (b) TBAF, 87%. (c) (1) Dess-Martin ox.; (2) CH_2=$CHCH_2PPh_3Br$, ^{t}BuOK; (3) *p*TsOH, MeOH, 23% (3 steps). (d) Dess-Martin ox., 83%. (e) (1) Swern ox.; (2) Ph_3P=$CHCO_2Et$; (3) DIBAL-H, 30% (3 steps). (f) (1) Dess-Martin ox.; (2) Ph_3PCH_3Br, BuLi; (3) *p*TsOH, MeOH, 33% (3 steps). (g) Dess-Martin ox., 86%. (h) (1) Dess-Martin ox.; (2) CH_3CH=$CHCH_2PPh_3Br$, (3) *p*TsOH, MeOH, 46% (3 steps). (i) Dess-Martin ox., 86%.

Initially, the cyclization of **15**, which does not have a methyl group on the terminus of the 1,3-diene moiety, was carried out under similar conditions, and the indolizidine derivatives **18a** and **19a** were obtained in yields of 40% and 38%, respectively.[10] Unfortunately, the use of Ph_3SiH did not improve the ratio of **18b** to **19b** in the construction of the indolizidine skeleton. To investigate whether the stereoisomers of the cyclized product were produced from the geometric isomers with regard to the 1,3-diene moiety in **15**, the cyclization of ***15E*** was examined. As a result, **18a** and **19a** were obtained in the same ratio as in the cyclization of **15**, which indicates that the geometry of the 1,3-diene moiety does not affect the stereochemistry of the cyclized

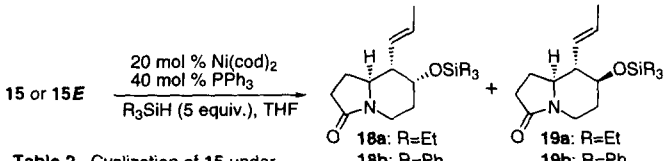


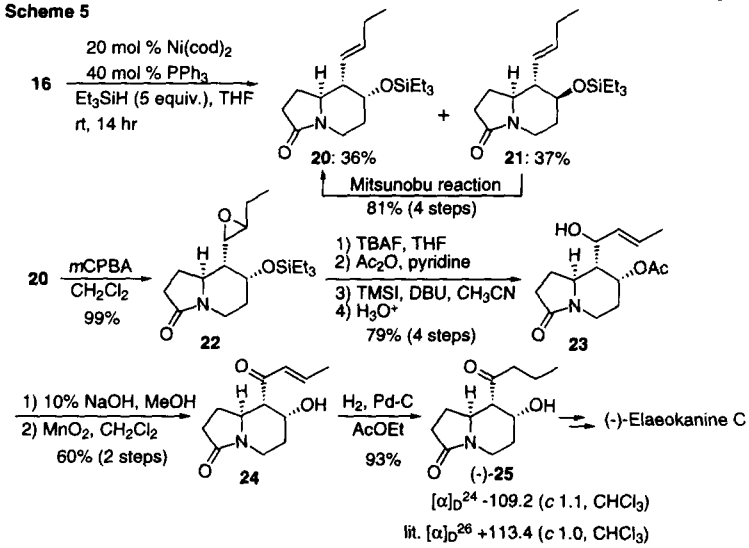
Table 2. Cyclization of **15** under the various conditions

run	substrate	R_3SiH	temp	time (hr)	yield (%) **18**	**19**
1	**15**	Et_3SiH	rt	12	40	38
2	**15**	Ph_3SiH	0 °C	1	39	43
3	**15*E***	Et_3SiH	rt	12	42	40

product. However, we were pleased to find that **19a** was easily transformed into the desired **18a** in 80% yield (4 steps) *via* Mitsunobu inversion.[11]

Next, the cyclization of **16**, which has a methyl group on the 1,3-diene moiety, was examined for the synthesis of (-)-Elaeokanine C. (Scheme 5) As expected, the indolizidine derivatives **20** and **21** were obtained in good yields, and the conversion of **21** to **20** was achieved in 81% yield (4 steps). Thus, we tried to synthesize (-)-Elaeokanine C from **20** (Scheme 5). Epoxidation of **20** with *m*CPBA gave epoxide **22** as two inseparable diastereomers. Attempts to rearrange epoxide **22** into the allyl alcohol were fruitless, perhaps due to the bulkiness of the triethylsilyl group. After the triethylsilyl group was replaced by an acetyl group, treatment with TMSI-DBU[12] followed by acidic work-up gave the desired allyl alcohol **23** in 79% yield (4 steps). Deprotection of the acetyl group followed by selective oxidation of the allylic alcohol gave enone **24** as a sole product, which was successively subjected to catalytic hydrogenation with Pd-C to produce (-)-**25**. The total synthesis of (+)-Elaeokanine C (unnatural antipode) from (+)-**25** has been previously reported by Koizumi and co-workers,[9j,k] and all of the spectral data of the synthetic (-)-**25** were identical to those reported for (+)-**25**, except for the sign of $[\alpha]_D$.

Scheme 5



$[\alpha]_D^{24}$ -109.2 (*c* 1.1, $CHCl_3$)

lit. $[\alpha]_D^{26}$ +113.4 (*c* 1.0, $CHCl_3$)

In conclusion, pyrrolizidine and indolizidine skeletons were successfully constructed by the nickel-catalyzed cyclization of 1,3-diene and aldehyde in a chain. In addition, we applied this method to the formal total synthesis of (-)-Elaeokanine C, which is the first synthesis of this compound in the naturally occurring form. Further studies along these lines are in progress.

References and Notes

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3. The enantiomeric purity of **7** was determined to be over 99% ee by HPLC analysis (DAICEL CHIRALCEL OD, hexane/^{i}PrOH=9/1). Since the enantiomeric purity of the aldehyde **8** could not be determined directly by HPLC analysis, reduction of **8** with $NaBH_4$ gave the alcohol **7**, again with over 99% ee, which indicates that no epimerization occurred during conversion of **7** into **8**.
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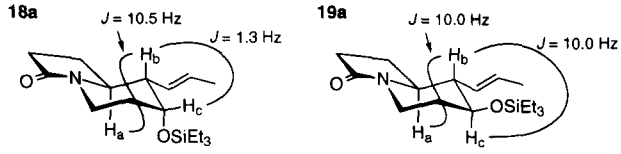
10. The stereochemistries of **18a** and **19a** were determined by the coupling constants of H_a and H_b, or H_b and H_c from the NMR spectra of **18a** and **19a**, respectively.



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