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[A0048]

Total Synthesis of Morphine- and Hasubanane Alkaloids

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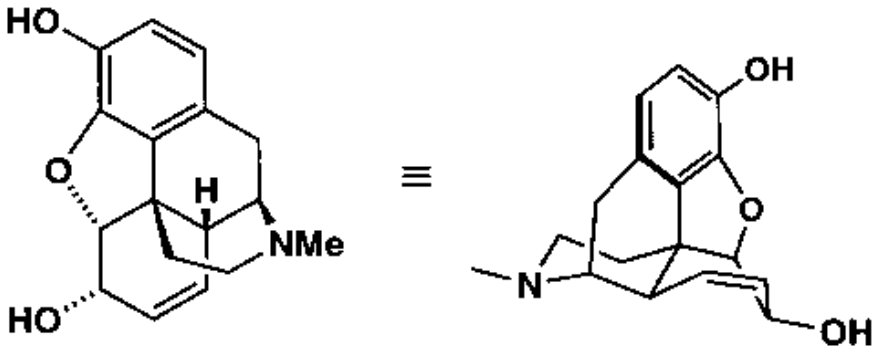
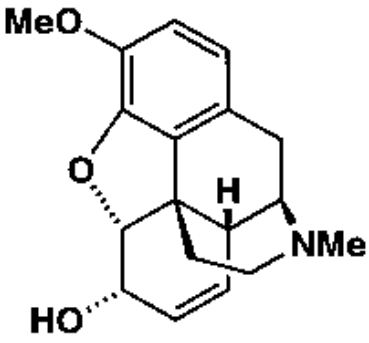
1. Introduction

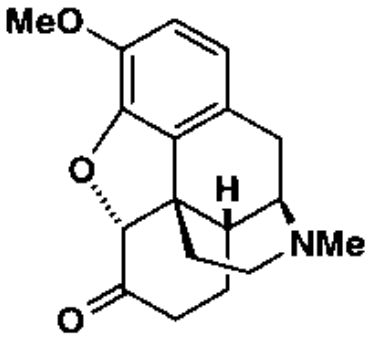
(-)-Morphine, the main alkaloid of the opium poppy, remains one of the most important medicines for the treatment of severe pain and a true delight for synthetic chemists.[1] In spite of its small size and long history, it is still considered to be an interesting target for chemical synthesis. (-)-Morphine and its synthetic precursors (-)-codeine and (-)-dihydrocodeinone feature a complicated network of three carbocycles and two heterocycles containing five vicinal stereocenters, four of which define ring junctures. Among these, the benzylic quaternary carbon deserves special attention.



(-)-morphine



(-)-codeine



(-)-dihydrocodeinone

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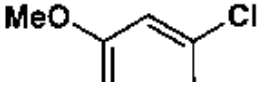
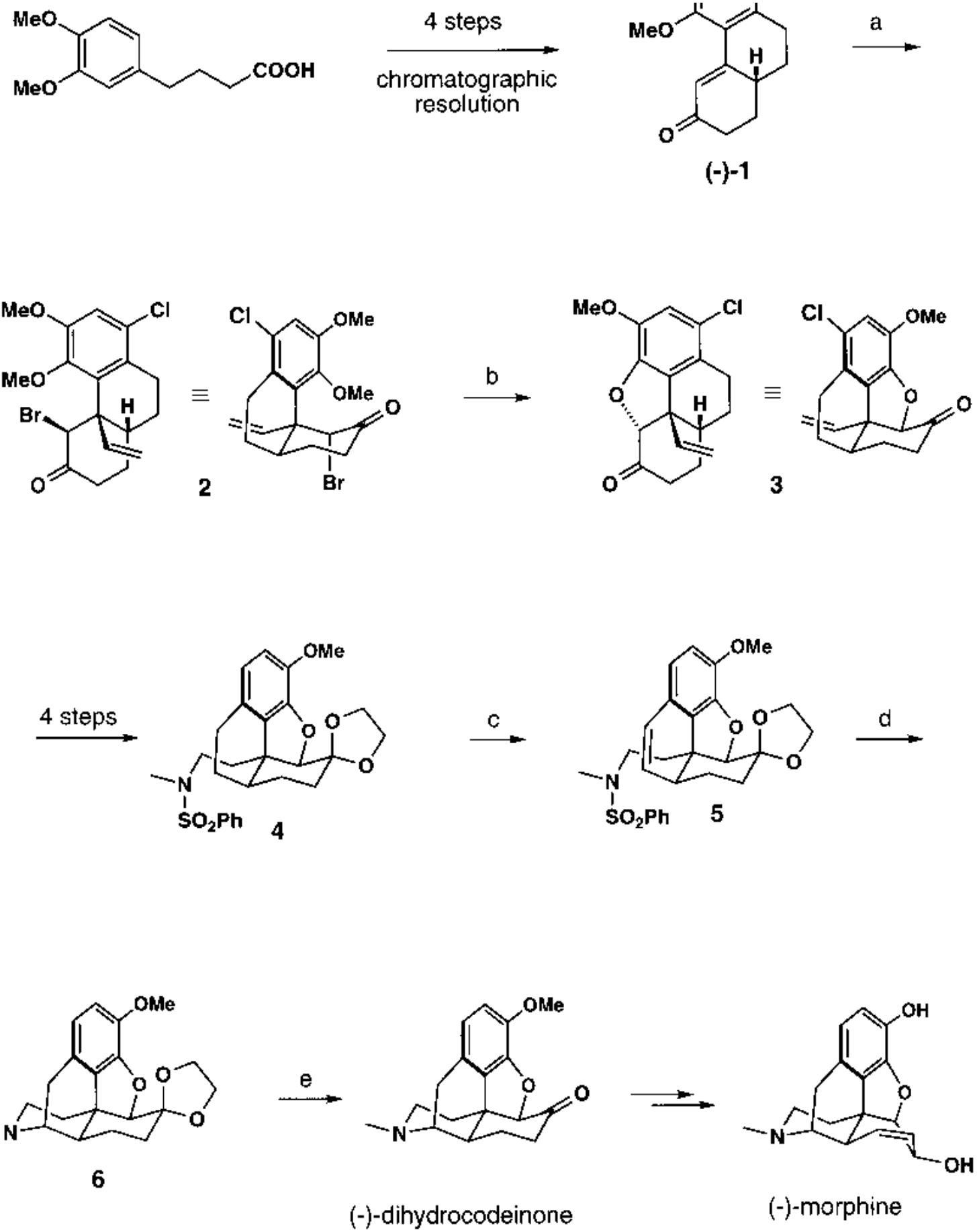
2. Formal Total Synthesis of (-)-Morphine by Cuprate Conjugate Addition[2]

Recently, we have reported an asymmetric formal total synthesis of (-)-codeine and (-)-morphine which features the conjugate addition of a simple vinyl cuprate to the optically pure enone **1**, followed by enolate trapping with *N*-bromosuccinimide (NBS) (Scheme 1). The X-ray crystal structure of the resultant bromoketone **3** is shown in Figure 1. Due to its conformational preorientation, **3** underwent particularly facile S_N2 ring-closure with concomitant demethylation to afford the tetracyclic ketone **3**. Ketone **3** was then transformed to sulfonamide **4** which was dehydrogenated by benzylic bromination / dehydrobromination to furnish the styrene **5** (Figure 2). On reductive desulfonation, **5** underwent radical (or anionic) ring-closure to provide the ethylene ketal **6** (Figure 2). Deprotection of **6** finally yielded dihydrocodeinone, a standard synthetic precursor of the opium alkaloids.




MeO
MeO
COOH
4 steps
chromatographic resolution
MeO
H
O
a
(-)-1
MeO
Cl
MeO
Br
H
O
2
Cl
OMe
OMe
O
Br
b
MeO
Cl
O
H
O
3
Cl
OMe
O
O
4 steps
OMe
O
O
N
SO2Ph
4
c
OMe
O
O
N
SO2Ph
5
d
OMe
O
O
N
6
e
OMe
O
O
N
(-)-dihydrocodeinone
OH
O
N
OH
(-)-morphine

Scheme 1. a) $(H_2C{=}CH)_2CuMgCl$, THF, - 78 °C to 0 °C; ii) TMSCl, Et_3N, 0 °C to 25 °C; iii) NBS, THF (63-80%). b) DMF, 140 °C (99%). c) NBS, $(PhCOO)_2$, CCl_4, rflx (68 - 81%). d) Li, NH_3, THF, *t*-BuOH (79 %). e) 3 *N* HCl, 90 °C (95 %).

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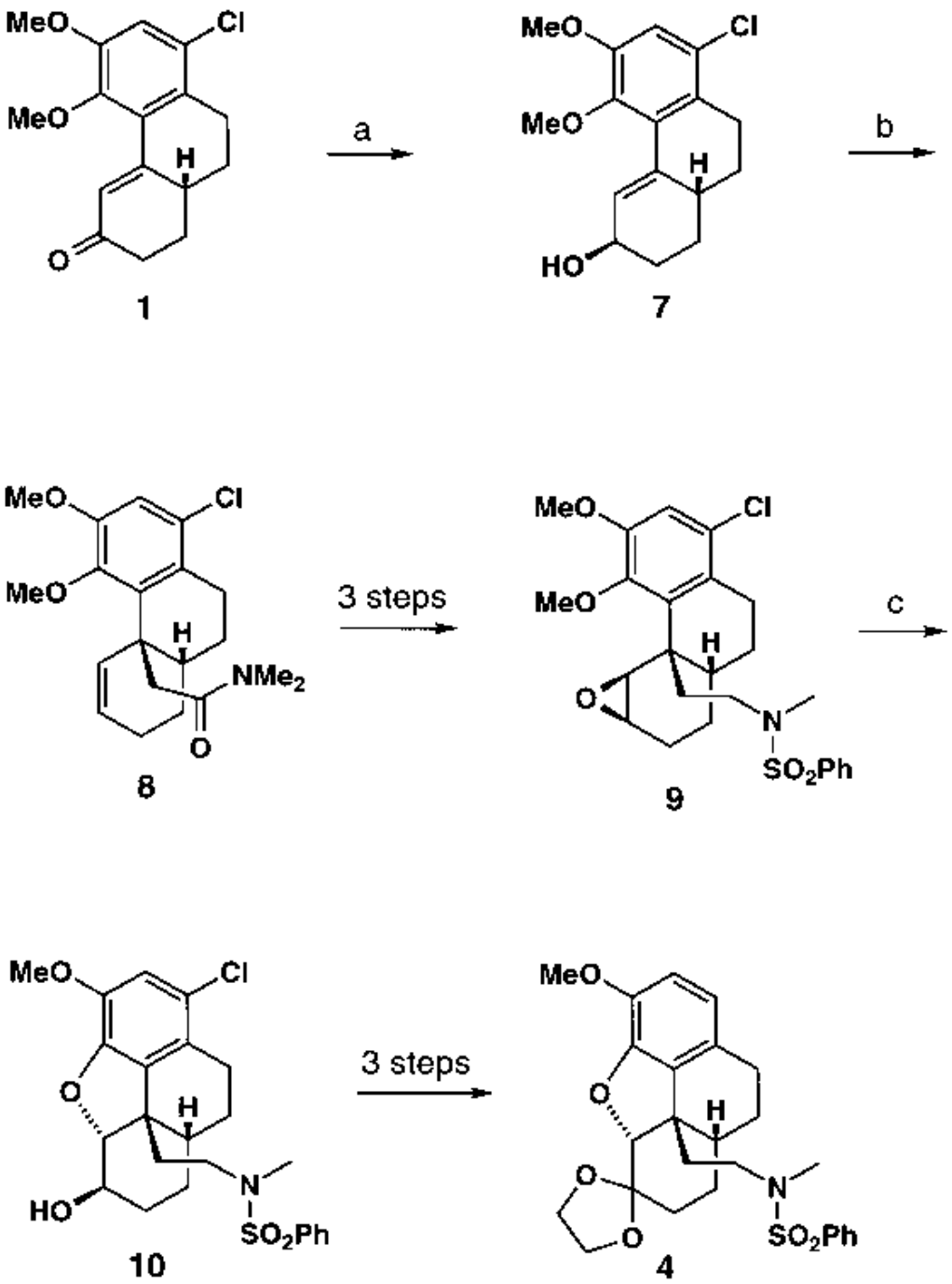
3. Synthesis *via* Eschenmoser-Claisen Rearrangement[3]

In addition to the cuprate chemistry we also used sigmatropic rearrangements to establish the benzylic quaternary stereocenter (Scheme 2). Diastereoselective reduction of **1** furnished the allylic alcohol **7** which underwent Eschenmoser-Claisen rearrangement to afford amide **8**. Modification of the C_2-side chain of **8**, followed by diastereoselective epoxidation, then gave sulfonamide **9**. Treatment of **9** with trifluoroacetic acid (TFA) in dry THF effected the desired ring closure with concomitant demethylation and provided the secondary alcohol **10**. Finally, **10** was converted into the secomorphinane **4**, thereby intercepting our previous synthetic route.



Scheme 2. a) DIBAH, THF, -78 °C (80%). b) *N,N*-Dimethyl-acetamide dimethyl acetal, PhMe, reflux (64%). c) TFA, THF, r.t. (83%).

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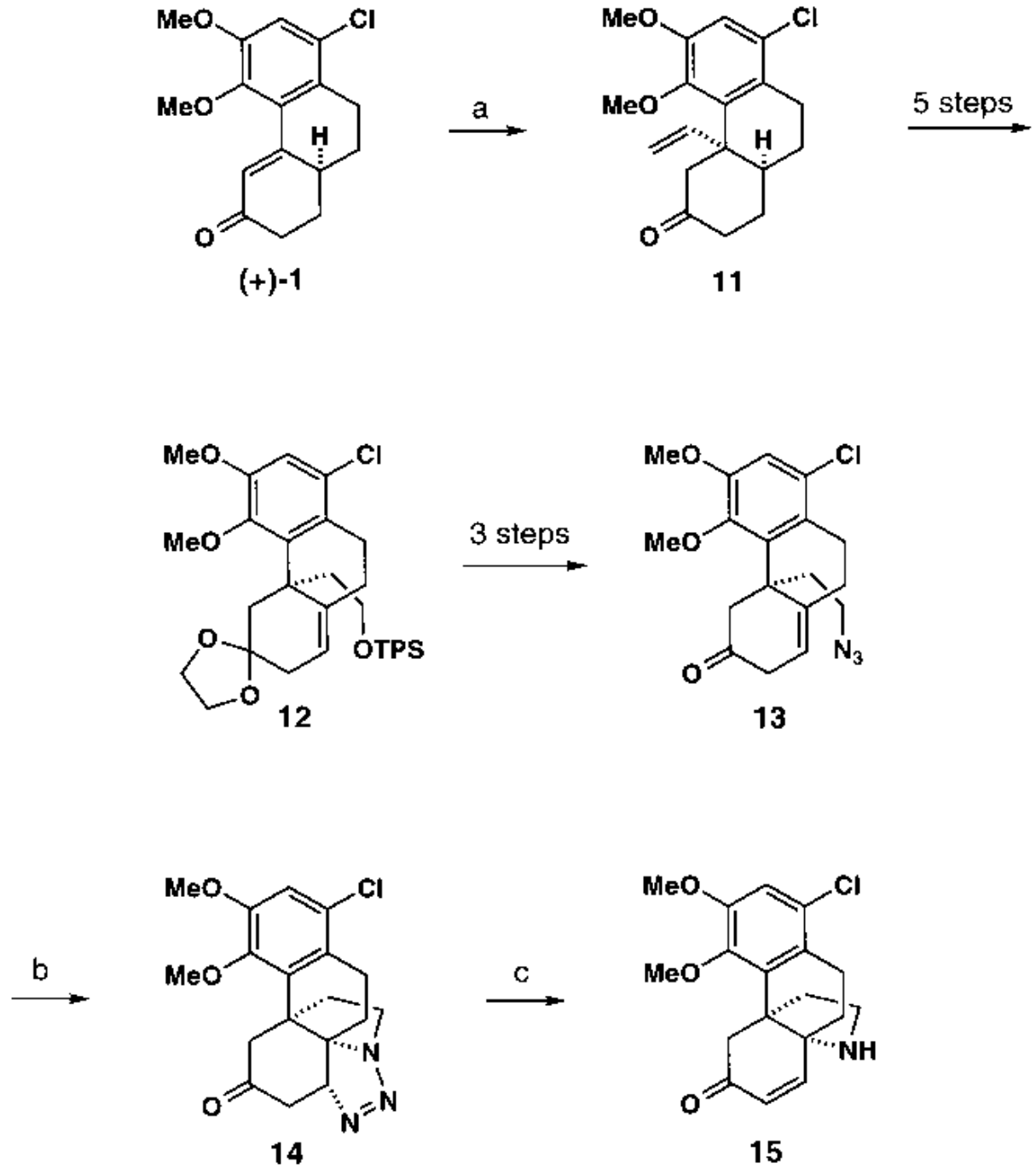
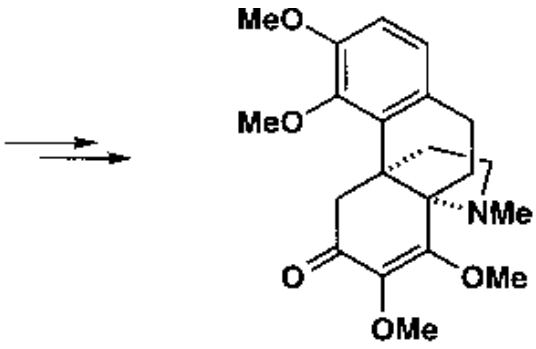
4. Synthesis of the Hasubanane Skeleton.

Our organocuprate strategy was also applied to the synthesis of hasubanane alkaloids which differ from morphine alkaloids mainly in their pyrrolidine ring (Scheme 3). The conjugate addition of a vinyl cuprate to phenanthrenone **1** - shown here as its (+)-enantiomer - afforded the ketone **11** which was converted to the azidoalkene **13** *via* compound **12**. On heating, **13**

underwent clean intramolecular 1,3-dipolar cycloaddition to furnish triazolidine **14**. The X-ray crystal structure of **14** in the form of its ethylene ketal is depicted in Figure 3. Treatment of **14** with base resulted in elimination of nitrogen and provided the amino-enone **15** which contains the complete hasubanane skeleton. The refinement of this strategy and the completion of the synthesis of (-)-hasubanonine are currently being pursued in our laboratories.





(-)-hasubanonine

Scheme 3. a) $(H_2C{=}CH)_2CuMgCl$, THF (91%). b) PhH, D (82%). (c) Py, D (75%).

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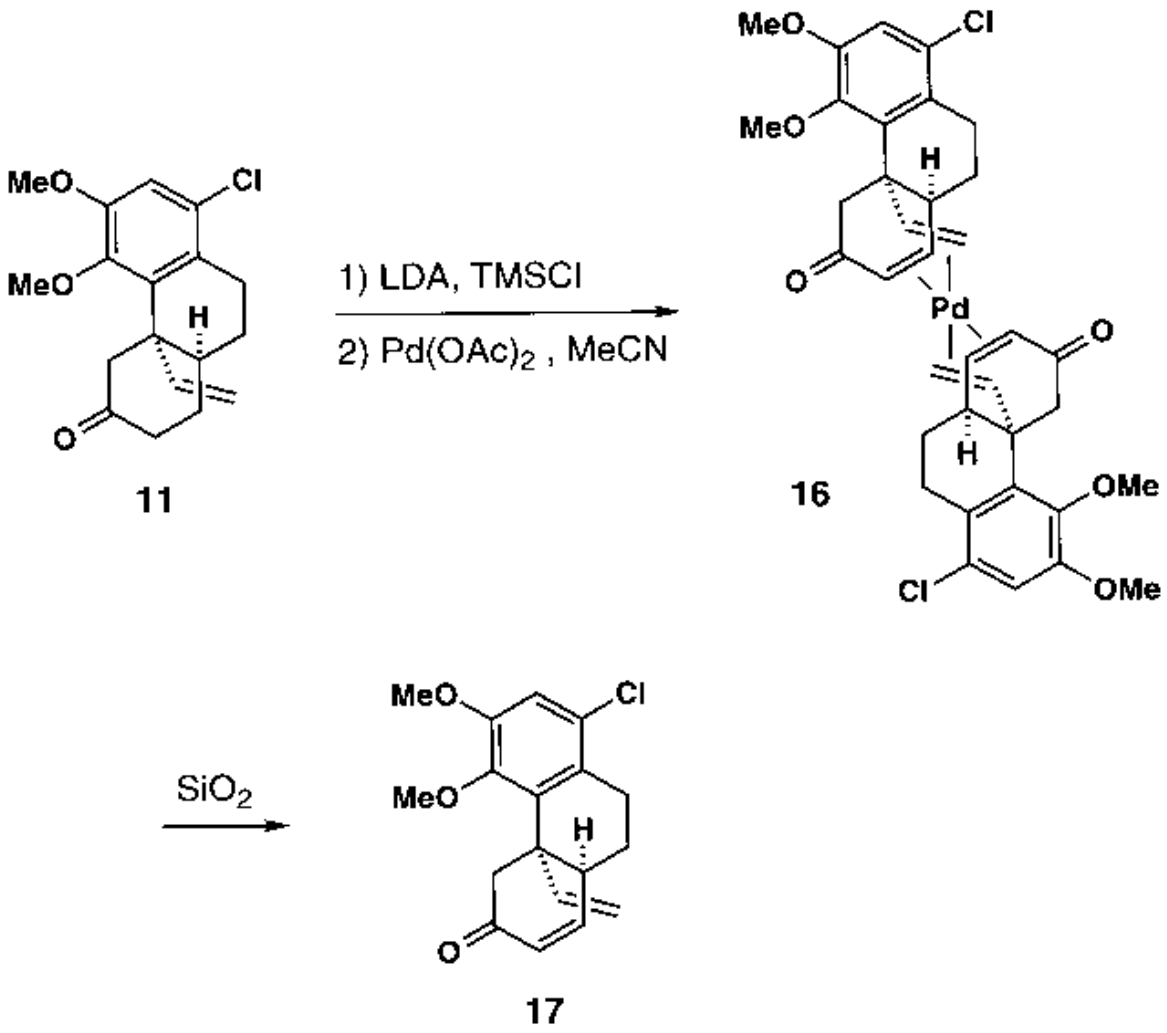
5. A Vinyl Residue Takes Over !

The Saegusa-oxidation of ketone **11** initially yielded the novel palladium(0)-enone complex **16**. Upon silica gel-chromatography, the expected enone **17** was liberated. The structure of **16** in the crystal is shown in Figure 4.



Scheme 5

6. Acknowledgment

We thank K. Högenauer for preparing the HTML version of this poster.

7. References

1. For reviews of the total synthesis of morphine alkaloids, see: a) Hudlicky, T.; Butora, G.; Fearnley, S.P.; Gum, A.G.; Stabile, M.R. in *Studies in Natural Products Chemistry* (*Ed.*: Atta-ur-Rahman); Vol. 18, p. 43; Elsevier: Amsterdam **1996**. b) Maier, M. in *Organic Synthesis Highlights II* (*Ed.*: Waldmann, H.); p. 357; VCH: Weinheim **1995**.

2. Mulzer, J.; Dürner, G.; Trauner, D. *Angew. Chemie Int. Ed. Engl.* **1996**, *35*, 2830 [*Angew. Chemie* **1996**, *108*, 3046].

3. Mulzer, J.; Bats, J.W.; List, B.; Opatz, T.; Trauner, D. *Synlett* **1997**, 441.

Comments

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