Pergamon

Tetrahedron Letters 41 (2000) 2043–2046

TETRAHEDRON LETTERS

A novel face specific Mannich closure providing access to the saframycin-ecteinascidin series of piperazine based alkaloids

Bishan Zhou,[a] Jinsong Guo [a] and Samuel J. Danishefsky [a,b,*]

[a]*The Department of Chemistry, Columbia University, Havemeyer Hall, New York, NY 10027, USA*

[b]*The Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., New York, NY 10024, USA*

Received 7 July 1999; revised 17 December 1999; accepted 19 December 1999

Abstract

The Mannich-like closure of **10→6** directly provides the backbone stereochemistry required for the titled alkaloids, in contrast to the stereochemical outcome in a related earlier case (**3→4**).

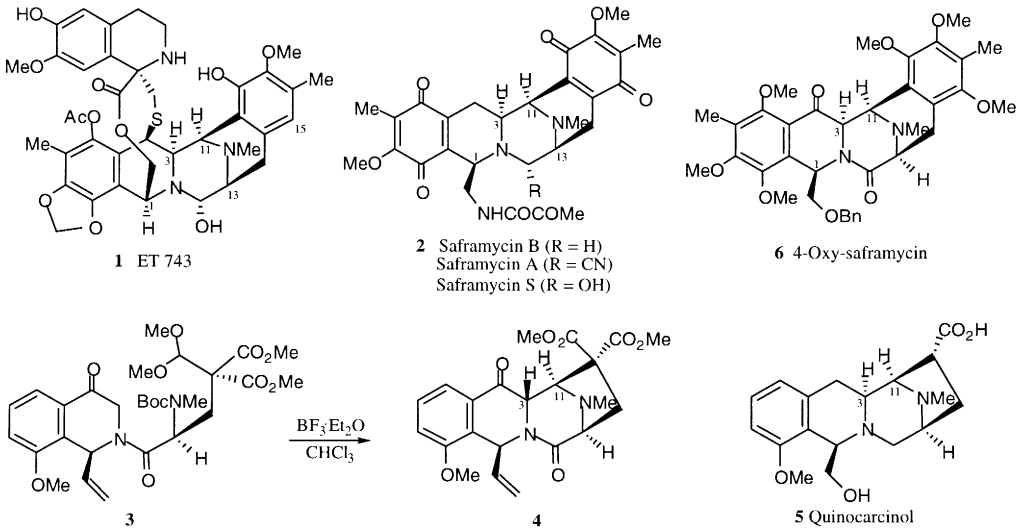
In the previous letter[1] we described the synthesis of two building blocks (vide infra) which would be merged and interlocked as part of a synthetic entry to the saframycin series antibiotic antitumor alkaloids (see representative structures **2**, Scheme 1).[2] Our underlying targets in this program are the ecteinascidins,[3] a family of highly potent cytotoxic agents (see representative ET structure **1**). The total synthesis of **1** by Corey and co-workers was the first and only synthesis of an ecteinascidin.[4]

In addition to the incentives for total synthesis, driven by the novel structures and highly potent antitumor properties of ET (**1**),[5] another interest in the group of piperazine based alkaloids arose from our total synthesis of quinocarcinol **5**.[6] The key to that construction, conducted long before the ET series was known, was a Mannich-like envelopment strategy (see **3→4**). In proposing to apply that lesson to the ET-saframycin family, we were not unaware that the *anti* backbone relationship between C3 and C11 in **4**, produced from **3**, required a stereochemical correction to reach the *syn* series of quinocarcinol. Such a C3–C11 *syn* relationship also pertains in **1** and **2**. We set as our goal compound **6**. In doing so, we would be revisiting the question of the reasons for the outcome of the backbone stereochemistry in the Mannich closure sequence.

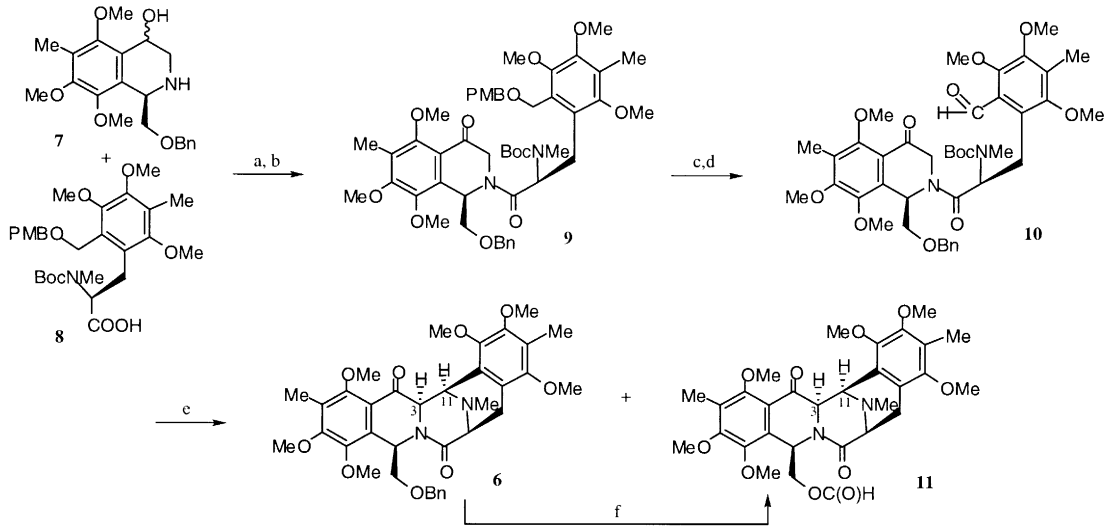
Coupling of **7** and **8** via amide bond formation was accomplished through the action of BOPCl,[7] as shown, in 60–65% yield (Scheme 2). Oxidation of the diastereomeric alcohol functions gave rise to **9** (75–80%) as a homochiral entity. To set the stage for the envisaged annulation, it was necessary to expose the aryl aldehyde function from its protected benzyl alcohol precursor. Following deprotection and oxidation, the homochiral **10**, bearing the strategic aldehyde,[8] was in hand.

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00106-4



Scheme 1.

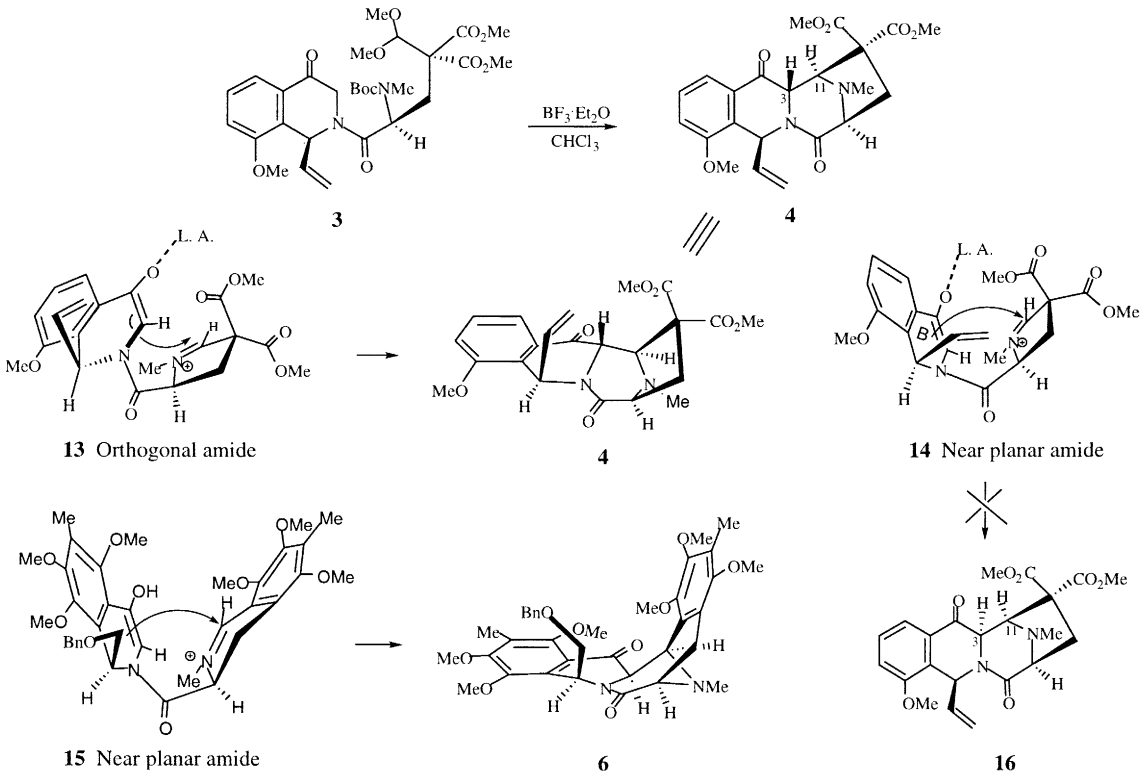


Scheme 2. (a) 1.1 equiv. BOPCl, 2.5 equiv. Et_3N, CH_2Cl_2, 10 h, 63%; (b) 1.5 equiv. Dess–Martin periodinate, CH_2Cl_2, 30 min, 78%; (c) 1.5 equiv. DDQ, CH_2Cl_2–buffer 7.0–H_2O (20:1:1), 3 h, 84%; (d) 2 equiv. NMO, cat. TPAP, m.s. 4 Å, CH_2Cl_2, 30 min, 84%; (e) formic acid, reflux, 10 h, 75% for **6**, 17% for **11**; (f) formic acid, reflux

In the event, exposure of compound **10** to the action of formic acid accomplished cleavage of the ^{t}Boc group, thereby triggering Mannich-like double closure to produce **6** (75%) and **11** (17%). These products differ only in the 'solvolytic' state of the primary center. In a subsequent step, **6** was converted to **11**. Characterization of **6** and **11** by extensive NMR measurements (including COSY, ROESY, HMQC and HMBC techniques) established an unexpected and most welcome result. Not only had cyclization occurred, but also the piperazinone ring had been elaborated with the *syn* C3–C11 backbone stereochemical relationship required for **1** and **2**.[9]

It is appropriate to conjecture about the strikingly different outcome in the seemingly similar ring closure steps of **3**→**4** and **10**→**6** (Scheme 3). We focus on the hypothetical iminium ions **13** and **15** which presumably appear in the two progressions. In each case, the system has been programmed such that

attack of the nucleophile can only occur from one face of the iminium electrophile (β-as drawn). The interesting issue arises with respect to the stereochemistry of the reaction of the nucleophile. If the enol is attacked from its α-face, the *anti* backbone will be produced (cf. **3**→**4**). Alternatively, attack from the β-face of the enol would give rise to a *syn* backbone product (**10**→**6**).



Scheme 3.

Aside from issues of steric hindrance, there is a potentially important stereoelectronic consideration. In modeling the closure reaction, it is seen that the coplanarity of the amide substituents can be maintained only if the enol is attacked from its β-face. By contrast, attack at the α-face of the enol seems to require rotation about the amide in the direction of orthogonalization. From this perspective the *syn* backbone cyclization product would be expected (see stereostructure **15**, which leads to **6**).

Comparable modeling soon reveals that in the case of hypothetical stereostructure **14**, which could also arise from **3**, attack at the β-face of the enol, though favored from the perspective of maximal maintenance of amide coplanarity, would incur a serious steric interaction between ring B and the two carbon bridge. This hindrance would be compounded by a particularly close abutment between the β-disposed vinyl and carbomethoxy groups if cyclization leading to the hypothetical **16** were to ensue. Hence, **4** rather than **16** is produced. By contrast, in **15**, where the six-membered iminium ring contains two additional sp^2 centers, the steric problems arising from the emerging *syn* backbone bridged system are perhaps reduced. In summary, it is proposed that cyclization of **10** (by way of stereostructure **15**) is governed by the stereoelectronic factor (maintenance of amide coplanarity), while cyclization of **3** (by way of stereostructure **13**), is dictated by an overriding steric hindrance effect, leading to **4**.

Research directed to testing our proposal on the interplay of the stereoelectronic and steric effects that

govern the critical Mannich step is ongoing in the context of our total synthesis and analog construction programs.[10]

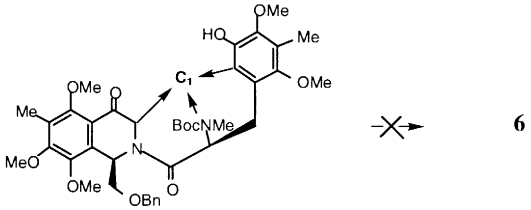
Acknowledgements

This work was supported by the National Institutes of Health (Grant Nos CA-28824 and HL-25848 (S.J.D.). B.Z. gratefully acknowledges the Pharmacia-Upjohn Corporation for a predoctoral Fellowship. We thank Vinka Parmakovich and Barbara Sporer (Columbia University) for mass spectral analyses.

Dedication. We dedicate this paper to Professor E. J. Corey and co-workers for their groundbreaking synthesis of Ecteinascidin 743 and for bringing this problem to our attention.

References

1. Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett*. **2000**, *41*, 2039.
2. (a) Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015. (b) Arai, T.; Takahashi, K.; Ishiguro, K.; Mikami, T. *Gann.* **1980**, *71*, 790.
3. Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 11456.
4. Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.
5. For recent reviews, see: (a) Pommier, Y.; Kohlhagen, G.; Bailly, C.; Waring, M.; Mazumder, A.; Kohn, K. *Biochemistry* **1996**, *35*, 13303. (b) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 3496.
6. Danishefsky, S. J.; Harrison, P. J.; Webb, R. R.; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421.
7. Cabre-Castellvi, J.; Polomo-Coll, A.; Palomo-Coll, A. C. *Synthesis* **1981**, 616.
8. Attempts to reach **6** by means of a 3-point attachment of a formic acid equivalent were unsuccessful. Only with the aromatic aldehyde in place was cyclization realized.



6

9. The stereochemistry assigned to **6** and **11** was verified by a crystallographic determination at a later stage of the synthetic sequence.
10. Subsequent studies reveal that the stereochemical outcome of the Mannich closure step is also a function of the substitution pattern on the aldehyde-containing aromatic ring that enters into the cyclization event. These matters will be discussed in a fuller treatment of the subject.