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Total Synthesis of Phorboxazole A via *de Novo* Oxazole Formation: Strategy and Componnent Assembly

Wang, B.; Hansen, T. M.; Wang, T.; Wu, D.; Weyer, L.; Ying, L.; Engler, M. M.; Sanville, M.; Leitheiser, C.; Christmann, M.; Lu, Y.; Chen, J.; Zunker, N.; Cink, R. D.; Ahmed, F.; Lee, C.-S.; Forsyth, C. J.* *J. Am. Chem. Soc.* **2011**, *133*, 1484-1505.

Total Synthesis of Phorboxazole A via *de Novo* Oxazole Formation: Convergent Total Synthesis

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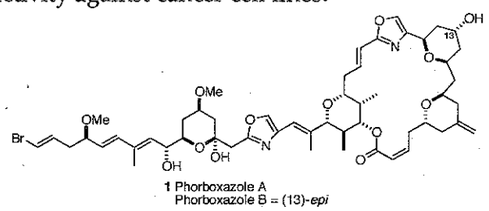
1. Introduction — Phorboxazole A and B

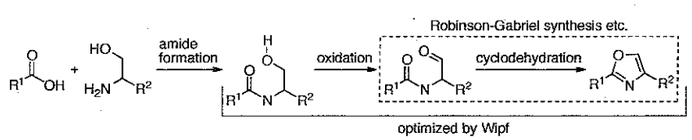
- Phorboxazole A and B were isolated from the Indian Ocean marine sponge Phorbas sp. in 1995.[1]
- They have novel structure and high cytostatic activity against cancer cell lines.
- First total synthesis of phorboxazole A was achieved by these authors in 1998.[2]
- Total synthesis of phorboxazoles is challenging due to its contiguous stereogenic centers and cis- and trans-substituted bis-oxane moiety.



1 Phorboxazole A
Phorboxazole B = (13)-*epi*

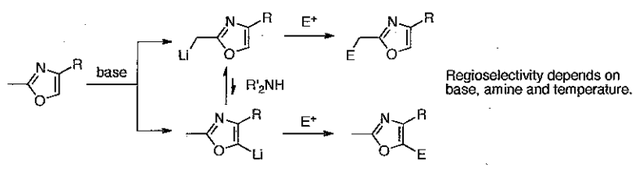
- This paper is the ninth total synthesis of phorboxazoles. These authors utilized the oxidation-cyclodehydration process[3] to construct oxazole (Scheme 1) in this work and in 1998, while the other 7 works incorporated presynthesized oxazole moieties.

Scheme 1. oxazole formation



- Functionalization of oxazoles is sometimes troublesome (Scheme 2).[4]

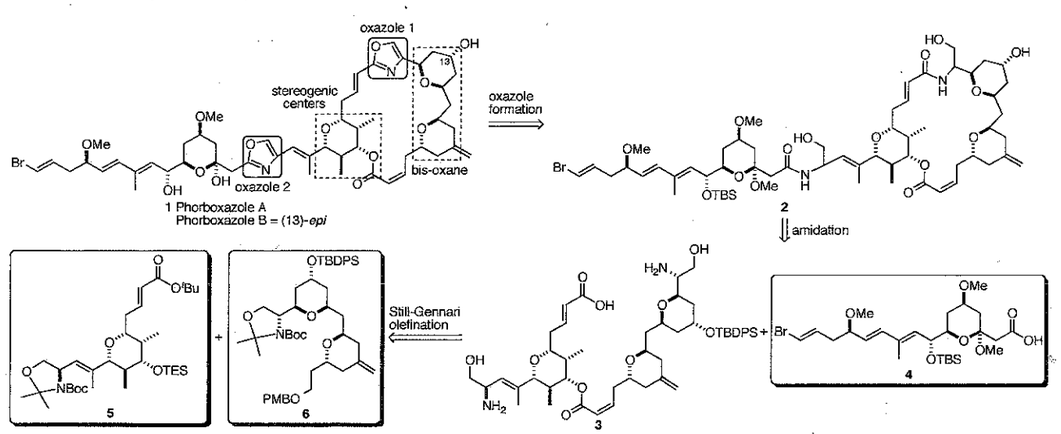
Scheme 2. Lithiation of oxazole



This work: (Scheme 3)

- Simultaneous oxazole formation in order to make the synthetic route concise and more efficient.
- Coupling of fragments **4**, **5** and **6**.

Scheme 3. Retrosynthesis for phorboxazole A

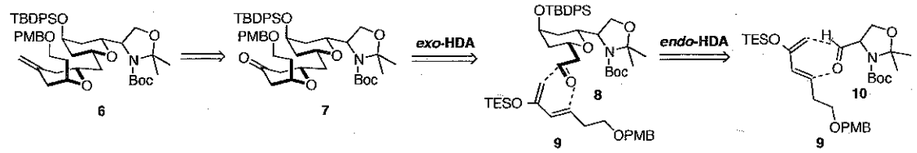


2. Results and Discussion

2-1. Synthesis of fragment 6 (Scheme 4)

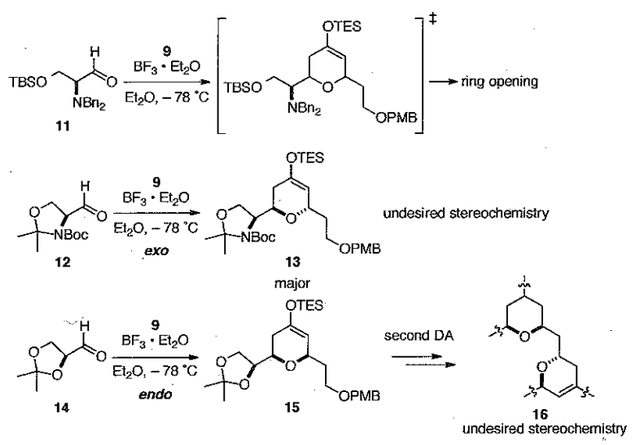
- Retrosynthesis for fragment **6** (key: iterative hetero Diels-Alder reaction)

Scheme 4. Retrosynthesis for fragment **6**



- Failed attempt to synthesize **6** (Scheme 5)

Scheme 5. HDA reaction with various substrates

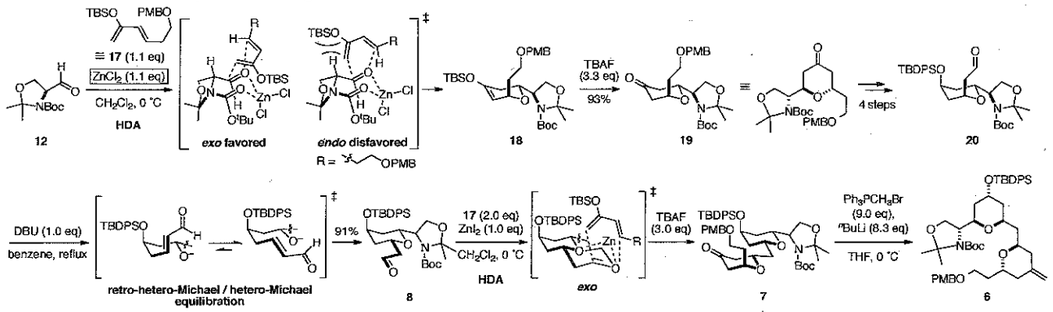


None of the screened conditions (Lewis acids, solvents and temperatures) afforded desired stereochemistry.

- Succeeded synthesis of fragment **6**

Bidentate Lewis acid assisted *exo*-selective Diels-Alder reaction and following base-induced epimerization was adopted. Fragment **6** was synthesized in ca. 39% yield over 10 steps from known intermediate Garner's aldehyde **12** (Scheme 6).

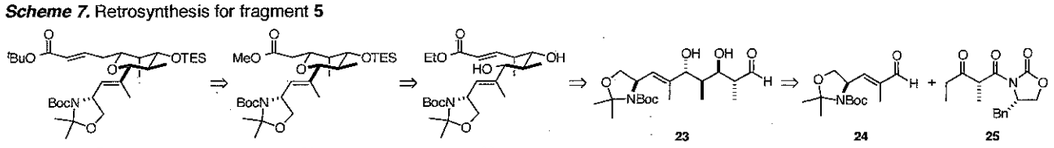
Scheme 6. Succeeded synthesis of fragment **6**



2-2. Synthesis of fragment 5 (Scheme 7)

- Retrosynthesis for fragment **5** (key: Michael addition cyclization and stepwise Wittig reaction)

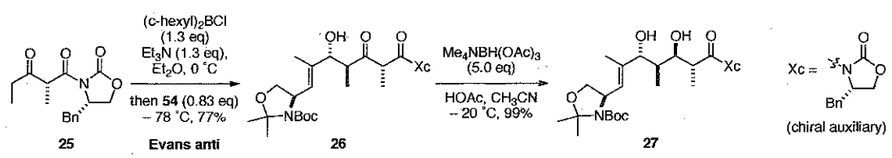
Scheme 7. Retrosynthesis for fragment **5**



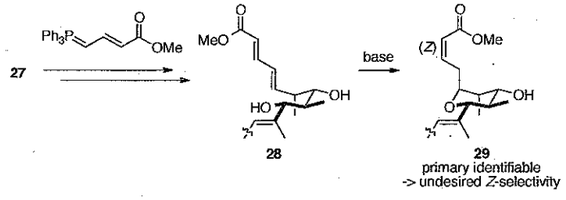
Evans aldol reaction was adopted to construct the desired stereochemistry.

• Synthesis of fragment **5** (Scheme 8)

Scheme 8. Evans aldol reaction and β -hydroxyl-directed reduction

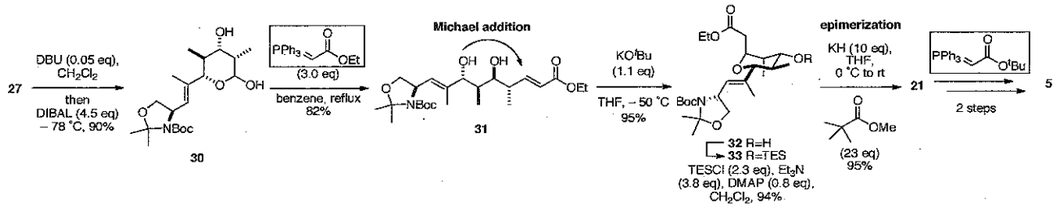


Scheme 9. Failed attempt to side chain introduction and cyclization



Introducing the side chain at once by Wittig reaction and cyclizing by Michael addition led to complex mixtures; among them, (Z)-acrylate was primarily identifiable (Scheme 9). Alternatively, the side chain was introduced in two times of Wittig reaction before and after the cyclization. Fragment **5** was synthesized in ca. 31% yield over 10 linear steps (Scheme 10).

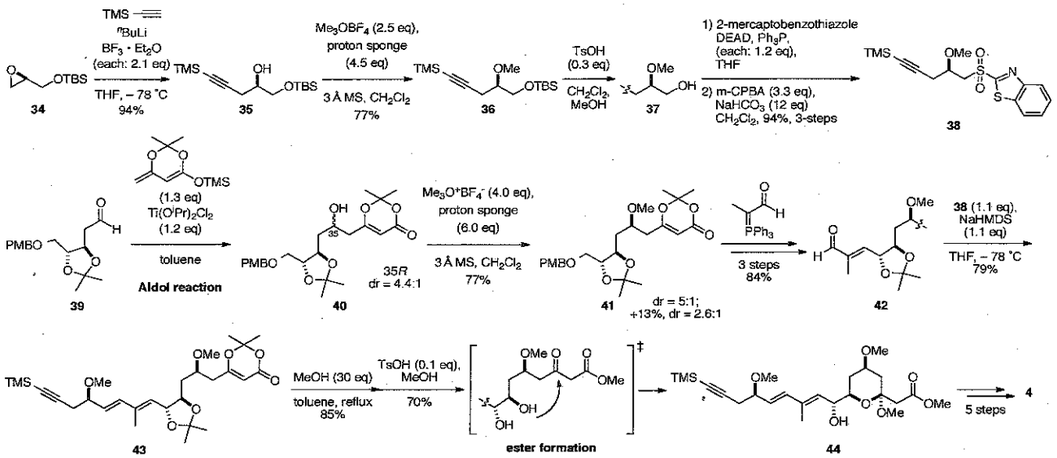
Scheme 10. Completion of the synthesis of fragment **5**



2-3. Synthesis of fragment 4 (Scheme 11)

• Synthesis of fragment 4 (key: diastereoselective aldol reaction and regioselective ester formation)

Scheme 11. Synthesis of fragment **4**



Fragment 4 was synthesized in ca. 11% yield over 13 steps.

2-4. Fragment coupling (Scheme 12)

Scheme 12. Coupling of fragments **4**, **5** and **6**

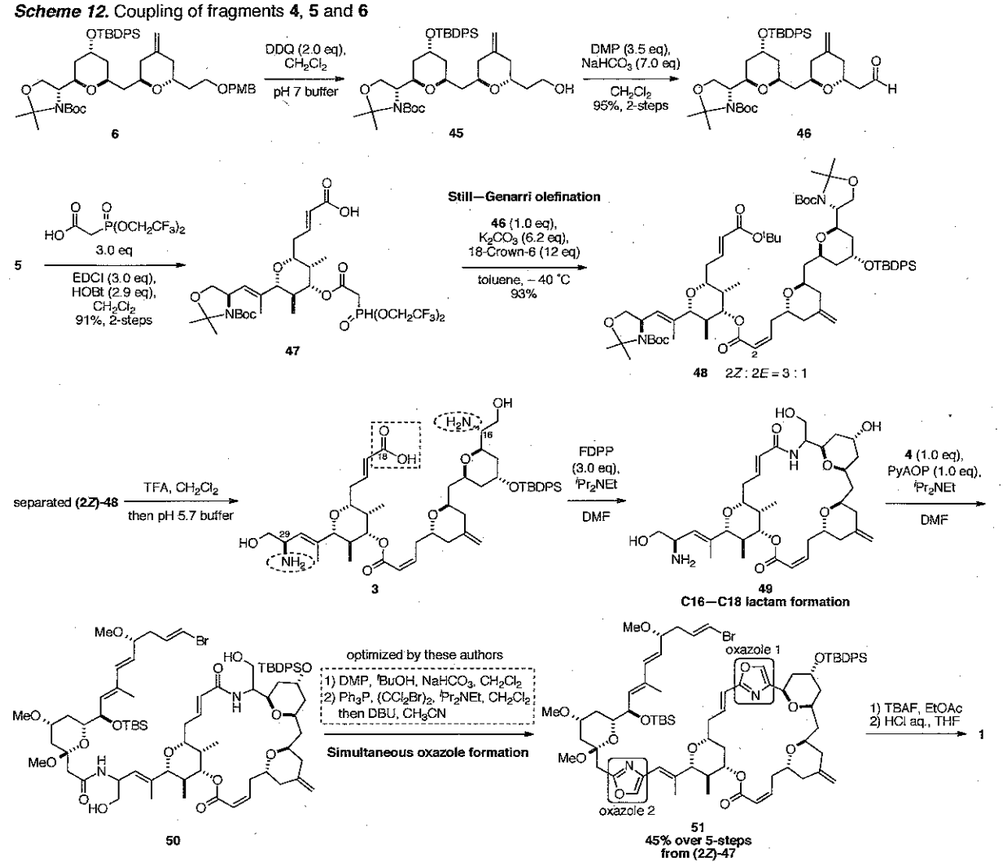


Table 1. Comparison of the efficiency of fragment coupling

	Yield (%)	Steps	Oxazole 1 (%)	Oxazole 2 (%)
First total synthesis	4.3	16	77	33
Optimized stepwise oxazole formation	15	15	91	71
Simultaneous oxazole formation	18	9	54	

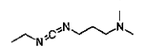
Three fragments were coupled in 18% over 9 steps and phorboxazole A was synthesized in ca. 2% overall yield in 22 steps in the longest linear sequence. Among these authors work, simultaneous oxazole formation afforded the highest yield and shortest steps to couple the three fragments (Table 1).

3. Conclusion

Concise and efficient fragment coupling to phorboxazole A has been achieved, which will be useful to synthesize analogues.

4. References

1. Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126-8131.
2. Forsyth, C. J.; Ahmed. F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597-5598.
3. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604-3606.
4. Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87-90.

Abbreviations TBS: *t*-butyldimethylsilyl, TBDPS: *t*-butyldiphenylsilyl, TES: triethylsilyl, TMS: trimethylsilyl, Boc: *t*-butoxycarbonyl, PMB: *p*-methoxybenzyl, TFA: trifluoroacetic acid, DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone DEAD: diethyl azodicarboxylate, NaHMDS: sodium *bis*(trimethylsilyl)amide, HOBt: 1-hydroxybenzotriazole, FDPP: pentafluorophenyl diphenylphosphinate, EDCI:  PyAOP: