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Synthesis of Enantiomerically Pure Desmethyl C,D-Ring Derivative of Paclitaxel (Taxol™) via Asymmetric Diels-Alder Reaction of 2-Siloxyfuran

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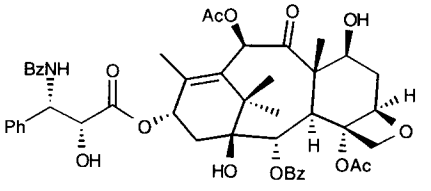
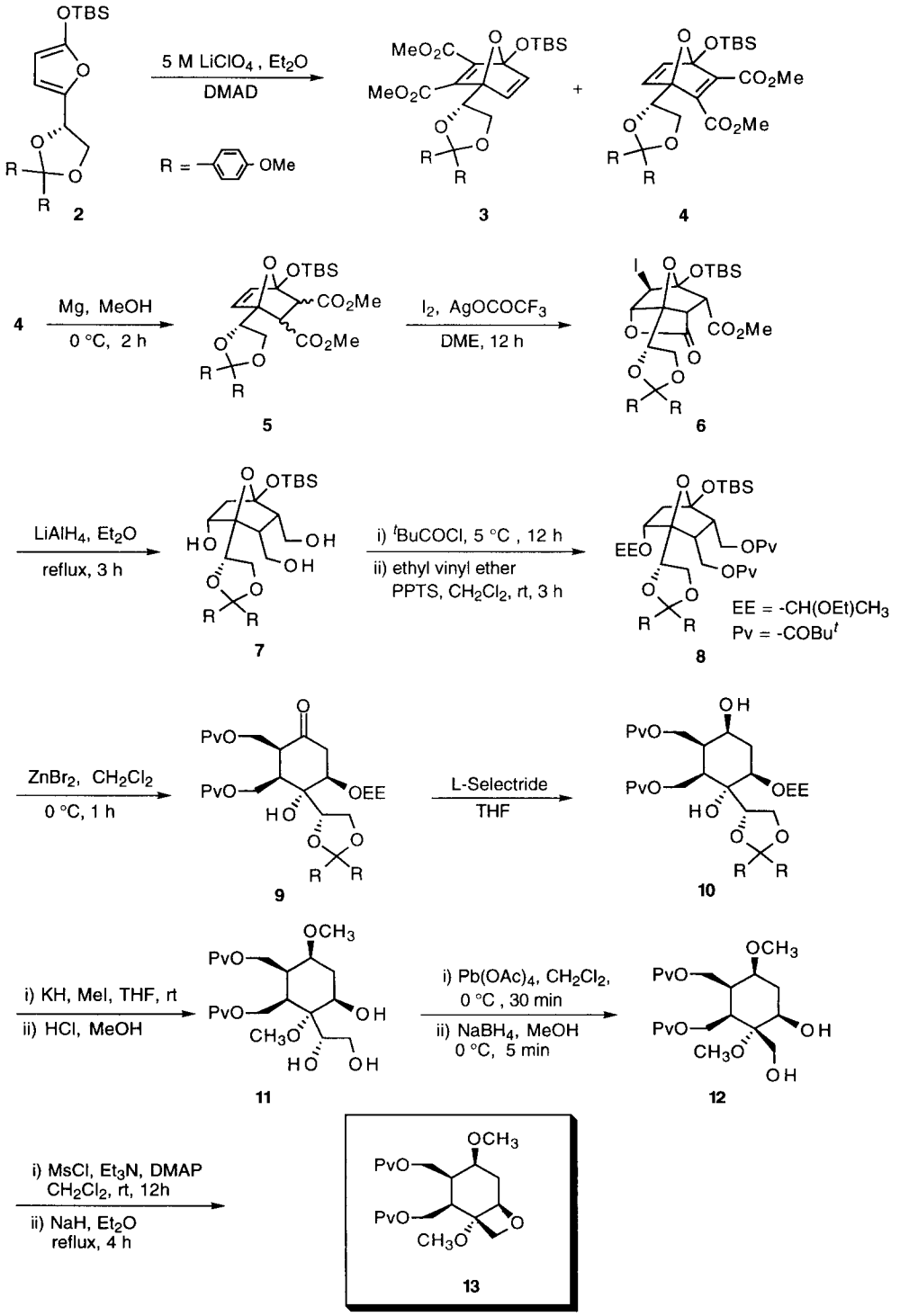
Abstract: Cycloadduct **3** of the asymmetric Diels-Alder reaction of 2-siloxyfuran **2** and dimethyl acetylenedicarboxylate was converted into the enantiomerically pure desmethyl C,D-ring derivative **13** of Paclitaxel. © 1997 Elsevier Science Ltd.

Paclitaxel (Taxol™) **1**, as a potent anti-cancer agent has been approved for the treatment of ovarian and breast cancers.[1] Evaluation for the treatment of other carcinomas is now being conducted in many institutions.[2] Not only due to its high therapeutic promise but also owing to its intricate molecular structure, paclitaxel has become one of the most attractive target for total synthesis in recent years.

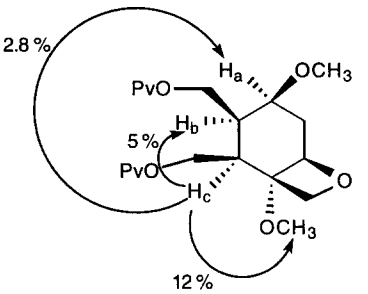


1

To date, three total syntheses of paclitaxel have been reported.[3] Several excellent reviews on the approaches toward the total synthesis of paclitaxel and its analogues have appeared.[4] In a typical convergent approach, A-ring and C,D-ring portions of paclitaxel were synthesized separately. These two portions were then coupled to construct the eight membered B-ring of the paclitaxel skeleton. Due to its stereochemistry and the presence of an oxetane subunit, the synthesis of the C,D-ring[4c,5] itself is a challenging problem. In our laboratories, we recently have developed a protecting-group-enhanced asymmetric Diels-Alder reaction of 2-siloxyfurans with high diastereofacial selectivity.[6] Herein we report the application of this asymmetric Diels-Alder reaction toward the synthesis of enantiomerically pure desmethyl C,D-ring derivative **13**.


OTBS
5 M LiClO4 , Et2O
DMAD
R = OMe
2
MeO2C
MeO2C
3
CO2Me
CO2Me
4
Mg, MeOH
0 °C, 2 h
5
I2, AgOCOCF3
DME, 12 h
6
LiAlH4, Et2O
reflux, 3 h
7
i) tBuCOCl, 5 °C , 12 h
ii) ethyl vinyl ether
PPTS, CH2Cl2, rt, 3 h
EEO
OPv
EE = -CH(OEt)CH3
Pv = -COBut
8
ZnBr2, CH2Cl2
0 °C, 1 h
PvO
OEE
9
L-Selectride
THF
10
i) KH, MeI, THF, rt
ii) HCl, MeOH
OCH3
CH3O
11
i) Pb(OAc)4, CH2Cl2,
0 °C , 30 min
ii) NaBH4, MeOH
0 °C, 5 min
12
i) MsCl, Et3N, DMAP
CH2Cl2, rt, 12h
ii) NaH, Et2O
reflux, 4 h
13

Asymmetric Diels-Alder reaction of 2-siloxyfuran **2**[7] with dimethyl acetylenedicarboxylate was carried out in 5 M lithium perchlorate ether solution[8] at room temperature to give cycloadducts **3** and **4** in excellent diastereofacial selectivity[9] (1:12, 83%). Cycloadducts **3** and **4** were separated readily by silica-gel flash column chromatography. Compound **4** was then treated with magnesium in methanol to give diesters **5** (*bis-endo-cis* isomer as the major product along with some minor *trans* isomer, 4:1). The mixture of diesters was treated with iodine and silver trifluoroacetate to afford iodo lactone **6** (82% from **4**). Reduction of iodo lactone **6** by lithium aluminum hydride yielded **7** (60%). Protection of the primary alcohols in **7** as the pivalates and the secondary alcohol as the ethoxyethyl ether gave compound **8** (96%). Removal of the *t*-butyldimethylsilyl group and cleavage of the oxygen bridge of **8** was effected by zinc bromide in dichloromethane at 0 ℃ to give ketone **9**. L-Selectride reduction of **9** yielded **10** (84% from **8**) with the desired stereochemistry. Double methylation of diol **10** by potassium hydride and iodomethane followed by deprotection with HCl in methanol gave triol **11** (86%). Oxidative cleavage of the vincinal diol in **11** by lead tetraacetate and subsequent reductive workup using sodium borohydride yielded compound **12** (90%). Methanesulfonation of **12** followed by the treatment with sodium hydride in refluxing diethyl ether produced the desmethyl C,D-ring derivative **13**[10] (84%). The stereochemistry of **13** was confirmed by ^{1}H NMR NOE experiment. Irradiation at H_c in **13** induces NOE at H_a (2.8 %), H_b (5 %) and α-OCH_3 (12 %) as shown below. This clearly indicated that the stereochemistry of H_a, H_b, H_c and α-OCH_3 are in *cis* relationship.



13

In summary, we have accomplished an efficient synthesis of enantiomerically pure desmethyl C,D-ring derivative **13** of paclitaxel via an asymmetric Diels-Alder reaction of 2-siloxyfuran **2**. We are currently investigating the stereoselective construction of paclitaxel framework by this approach in our laboratory.

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10. Data of compound **13**: $[\alpha]^{23}_D$ = -15.1° (c 0.5, $CHCl_3$). IR (neat) 2939, 1728, 1474, 1397, 1234, 1156, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 2.0, 6.8 Hz, 1 H), 4.53 (A of AB, d, *J* = 7.0 Hz, 1 H), 4.41 (B of AB, d, *J* = 7.0 Hz, 1 H), 4.37-4.26 (m, 4 H), 3.48 (m, 1 H), 3.30 (s, 3 H), 3.23 (s, 3 H), 2.33 (td, *J* = 5.2, 9.2 Hz, 1 H), 2.12 (ddd, *J* = 2.0, 4.2, 16.0 Hz, 1 H), 2.05 (tdd, *J* = 7.6, 2.4, 9.2 Hz, 1 H), 1.81 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.12 (C=O), 177.90 (C=O), 82.96 (CH), 76.46 (C), 74.54 (CH_2), 74.44 (CH), 63.27 (CH_2), 63.06 (CH_2), 56.60 (CH_3), 50.45 (CH_3), 38.84 (CH), 38.69 (C), 37.55 (CH), 31.56 (CH_2), 27.24 (CH_3). MS (FAB) *m/z* 401(M^++ H, 5), 299 (44), 165 (19), 135 (20), 85 (22), 57 (100). HRMS (FAB, M^+ + H) calcd for $C_{21}H_{37}O_7$ 401.2539, found 401.2549.

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