Pergamon

Tetrahedron Letters, Vol. 35, No. 43, pp. 7957-7960, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01688-7

A TOTAL SYNTHESIS OF (-)-REISWIGIN A VIA SEQUENTIAL CLAISEN REARRANGEMENT-INTRAMOLECULAR ESTER ENOLATE ALKYLATION‡

Deukjoon Kim[a]*, Kye Jung Shin[a], Ik Yoen Kim[a] and Sang Woo Park[b]

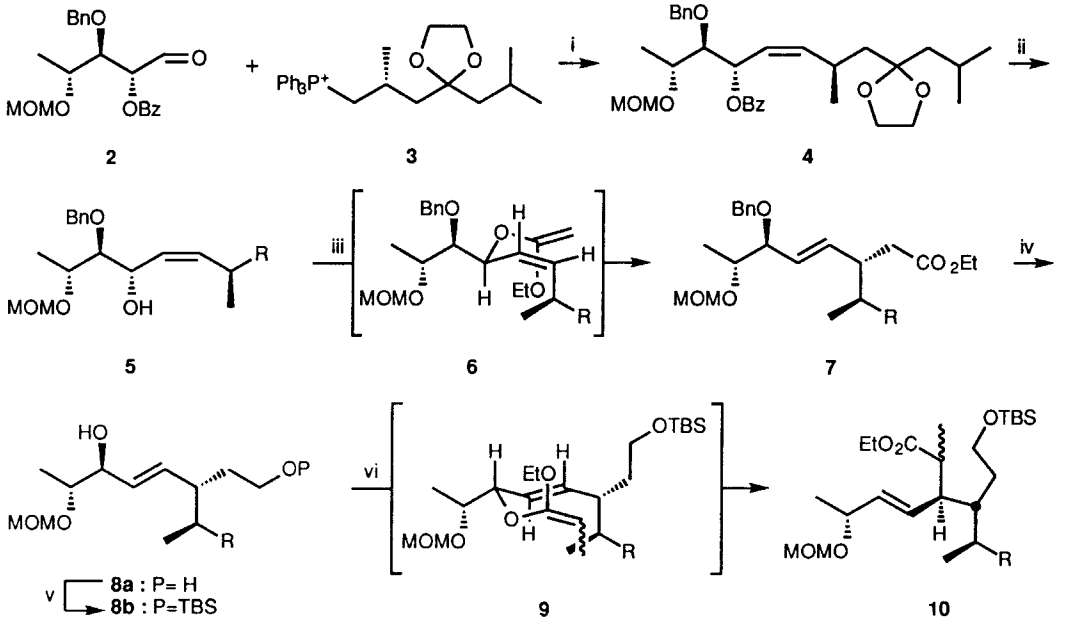
[a] College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151-742, Korea

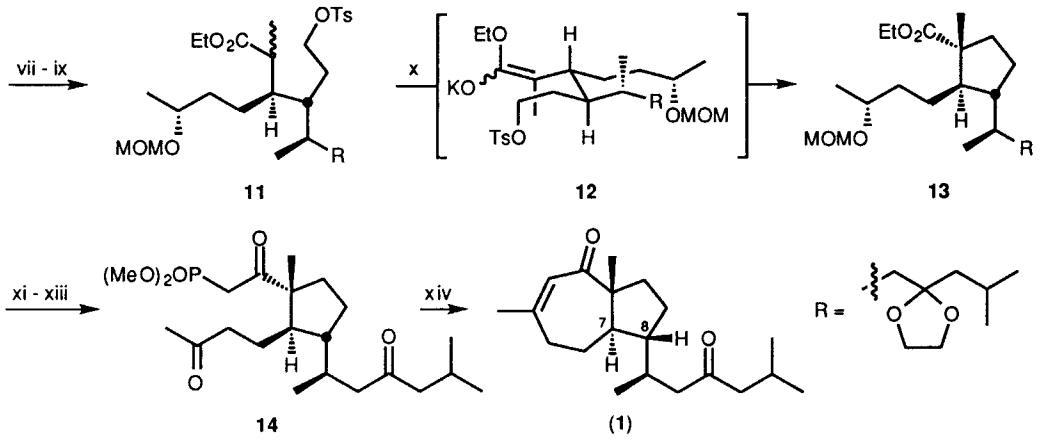
[b] Division of Chemistry, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea

Abstract: (-)-Reiswigin A (**1**), a novel anti-viral diterpene, has been synthesized in a highly stereoselective manner utilizing a sequential Claisen rearrangement - intramolecular ester enolate alkylation strategy.

(-)-Reiswigin A (**1**), recently isolated by Koehn and coworkers from a deepwater marine organism *Epipolasis reiswigi* collected by a submersible at 330 m, shows potent *in vitro* activity against Herpes simplex type I virus and murine A59 hepatitis virus.[1] The relative and absolute stereochemistry of (-)-reiswigin A was firmly established by an elegant synthesis by Snider and Yang.[2] Described herein is an asymmetric synthesis of (-)-reiswigin A (**1**) featuring a sequential Claisen rearrangement[3] [**5** -> **7** & **8** -> **10**] and our 'allylic strain-controlled'[4] and 'folding strain-controlled'[5] intramolecular ester enolate alkylation strategy [**11** -> **13**] as key steps as summarized in **Scheme I**.

Scheme I

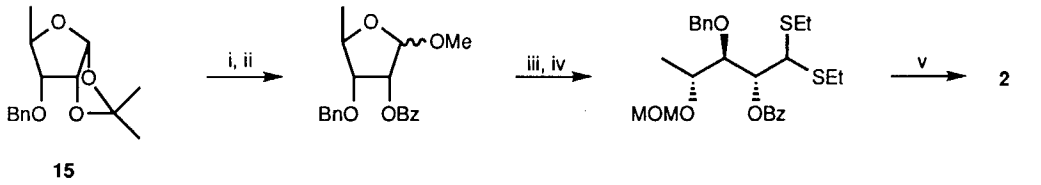




Reagents: i) *n*-BuLi (1.1 eq), THF, HMPA (1 eq), -78 °C, 3h, rt, 1h (62%); ii) anhydrous K_2CO_3 (2 eq), MeOH, 40 °C, 5h (95%); iii) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$ (cat.), 120 °C, 4h (93%); iv) Li (8 eq), NH_3 : THF : EtOH (3 : 1 : 1), -78 °C, 30 min (92%); v) TBSCl (1.1 eq), imidazole (1.5 eq), DMF, 0 °C, 2h, rt, 5h (95%); vi) $CH_3CH_2C(OEt)_3$, phenol (cat.), 130 °C, 3h (92%); vii) H_2 (60 psi), PtO_2 (0.1 eq), EtOH, TEA, rt, 3h (87%); viii) TBAF (2 eq), THF, rt, 2h (92%); ix) TsCl (1.5 eq), pyridine (2 eq), $CHCl_3$, rt, 18h (96%); x) KHMDS (5 eq), THF, -78 °C, 2h to -40 °C, 3h (92%); xi) $(MeO)_2POCH_2Li$, (15 eq), THF, -78 °C, 2h, -20 °C, 1h (90%); xii) c-HCl (cat.), MeOH, 60 °C, 1h (100%); xiii) PCC (2 eq), CH_2Cl_2, rt, 3h (92%); xiv) DBU (4 eq), CH_3CN, rt, 24h (85%).

The preparation of the requisite chiron aldehyde **2** was accomplished in five steps in 48% overall yield from readily available known D-xylose-derived carbohydrate precursor **15**[6] by well-established chemistry as outlined in **Scheme II**.[7]

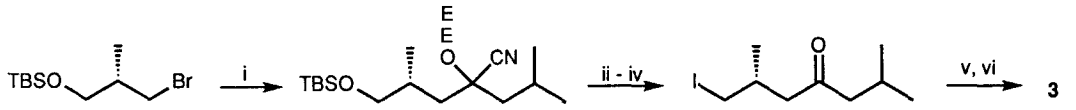
Scheme II



Reagents: i) 1% I_2 in MeOH, 60 °C , 1.5h (92%); ii) BzCl (1.5 eq), TEA (3 eq), CH_2Cl_2, rt, 10h (95%); iii) EtSH (4 eq), BF_3OEt_2 (2 eq), CH_2Cl_2, -20 °C, 3h (87%); iv) MOMCl (1.5 eq), Hunig's base (2 eq), CH_2Cl_2, 0 °C, 1h to rt, 15h (92%); v) I_2 (3 eq), $NaHCO_3$ (6 eq), acetone : H_2O (15 : 1), -20 °C, 1h (68%).

Wittig reagent **3** was synthesized starting from optically active bromide **16** via Stork's protected cyanohydrin alkylation technology[8] in eight operationally simple steps in 35% overall yield as illustrated in **Scheme III**. It is worthwhile to mention that attempts at forming the phosphonium salt from the dioxolane ketal derivative of ketone **17** were unsuccessful.[9]

Scheme III



16 17

Reagents: i) EEO(CN)CHCH$_2$CH(CH$_3$)$_2$ (1 eq), LDA (1.1 eq), HMPA (1 eq), THF, -78 °C, 2h to rt, 3h (85%); ii) TBAF (1.2 eq), THF, rt, 1h (85%); iii) TsCl (1.5 eq), pyridine (2 eq), $CHCl_3$, rt, 8h; iv) NaI, MEK, 80 °C, 3h (60% for 3 steps); v) 5% H_2SO_4 : MeOH (1 : 5), rt, 30 min; vi) 0.5-N NaOH, ether, 10 min (95% for 2 steps); vii) Ph_3P (1.2 eq), toluene, 110 °C, 10h (88%); viii) HOCH$_2$CH$_2$OH (2 eq), PTSA, benzene, 80 °C, 48h (82%).

Stereoselective Wittig reaction between aldehyde **2** and phosphonium salt **3** followed by saponification of the benzoate group of the resulting (Z)-olefin **4** produced the first Claisen rearrangement substrate **5** in 59% yield for the two steps. Upon heating with triethyl orthoacetate in the presence of catalytic amount of propionic acid, allylic alcohol **10** underwent a smooth Johnson orthoester Claisen rearrangement[10] to afford γ, δ-unsaturated ester **7,** presumably via a chair-like transition state geometry **6** in 93% yield. Reduction of the ester function with concurrent removal of the benzyl protecting group of compound **7** by treatment with lithium and ammonia, followed by selective mono-silylation of the primary hydroxyl group of the resulting diol **8a** furnished the second Claisen substrate **8b** in 87% overall yield for the two steps. Subjection of allylic alcohol **8b** to the sequential Claisen rearangement afforded ester **10,** probably through a six-membered transition state **9** in 92% yield.[7] Thus, the correct configuration at both C 8 and 7 of (-)-reiswigin A was firmly established by consecutive 1,3-chirality transfer processes. Catalytic hydrogenation of olefin **10** with PtO_2 in the presence of triethylamine, removal of TBS group with TBAF and tosylation produced key internal alkylation substrate **11** in 80% overall yield. Our 'allylic strain-controlled' and 'folding strain-controlled' intramolecular ester enolate alkylation of **11** with KHMDS in THF at -78 to -40 °C for five hours produced the desired cyclopentanecarboxylate **13** in 92% yield with excellent stereoselectivity,[7] probably through the preferred '*H-eclipsed*' transition state geometry **12**.[4] Cyclization product **13** was converted to (-)-reiswigin A (**1**) in four steps using an internal Horner-Wadsworth-Emmons reaction[11] as a key strategy. Thus, treatment of ester **13** with the lithium anion derived from dimethyl methylphosphonate[12] and simultaneous removal of both MOM and ketal protecting groups of the resulting keto phosphonate under acidic conditions, followed by PCC oxidation, afforded an internal Horner-Emmons substrate **14** in 83% overall yield for the three steps. Finally, ketophosphonate **2** underwent a smooth intramolecular olefination upon treatment with DBU to give an 85% yield of the desired (-)-reiswigin A (**1**) ($[\alpha]^{20}_D$ = -10.3°, c = 0.6, $CDCl_3$ (lit.[1] $[\alpha]^{20}_D$ = -10°, c = 0.1, $CDCl_3$)), whose spectral data was identical to those kindly provided by Drs. Snider and Koehn.[13]

In summary, an enantioselective synthesis of (-)-reiswigin A (**1**) has been accomplished with a very high stereochemical control via a sequential Claisen-IEEA route in 14 steps from carbohydrate-based chiral precursor **2**.[14] Efforts are being made to apply this strategy to asymmetric syntheses of structurally related biologically active cyclopentanoid natural products such as ceroplastol II[15] and albolic acid[16].

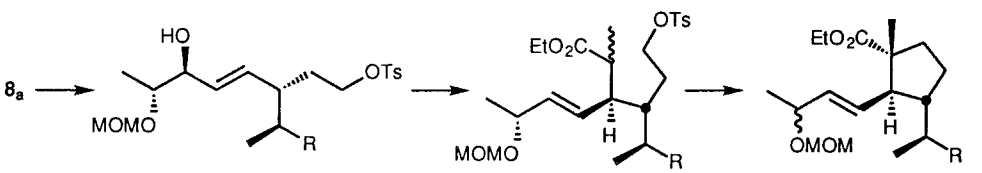
Acknowledgements: We gratefully acknowledge generous financial support from the KOSEF and the Organic Chemistry Research Center. We thank Ms. J. H. Kim and Mr. Y. K. Choi (Pharmacal Research

Institute, Seoul National University) for the measurement of high-field NMR and LRMS spectra. Combustion analysis and HRMS data were obtained from OCRC and Korea Basic Science Center, respectively.

References and Notes;

‡ This work was presented in part at 2nd KOSEF-INSA Joint Seminar on Natural Product Chemsitry, Seoul, Korea, November 23 -24, 1992, Abstracts, pp 13.

1. Kashman, Y.; Hirsh, S.; Koehn, F.; Cross, S. *Tetrahedron Lett.* **1987**, 28, 5461.
2. Snider, B. B.; Yang, K. *Tetrahedron Lett.*. **1989**, 30, 2465; Snider, B. B.; Yang, K. *J. Org. Chem.* **1990**, 55, 4392.
3. For elegant use of an acyclic sequential Claisen rearrangement strategy in natural product synthesis, see: Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, 100, 8272.
4. Ahn, S. H. ; Kim, D.; Chun, M. W.; Chung, W. *Tetrahedron Lett.* **1986**, 27, 943; Kim, D.; Lim, J. I.; Shin, K. J.; Kim, H. S. *Tetrahedron Lett.* **1993**, 34, 6557 and references cited therein.
5. Tokoroyama, T.; Okada, K.; Iio, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1572 and references cited therein.
6. Kiss, J.; D'Souza. R.; van Koeveringe, J.; Arnold, W. *Helv. Chim. Acta* **1982**, 65, 1522.
7. All new compounds exhibited satisfactory spectroscopic data. Compound **13** : The ratio of stereoisomers was determined by capillary glc analysis (0.2 mm i.d. x 17 m length SE-30). **IR** (Neat) 1724 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.94 (d, J = 6.8 Hz, 6H), 1.01 (d, J = 6.8 Hz, 3H), 1.08 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.23 (t, J = 7.3 Hz, 3H), 1.28 - 1.44 (m, 4H), 1.52 (d, J = 6.4 Hz, 2H), 1.45 - 1.61 (m, 3H), 1.64 - 1.81 (m, 5H), 1.95 (dt, J = 9.3, 12.2 Hz, 1H), 2.14 (dt, J = 4.4, 9.3 Hz, 1H), 3.35 (s, 3H), 3.59 (m, J = 6.4 Hz, 1H), 3.93 (br s, 4H), 4.11 (dq, J = 7.3, 2.4 Hz, 2H), 4.59 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.2, 17.4, 20.2, 22.0, 24.0, 24.0, 24.1, 24.6, 26.1, 29.8, 35.2, 38.6, 39.1, 45.6, 48.9, 50.9, 51.2, 55.2, 60.2, 64.3, 64.5, 73.5, 94.8, 12.6, 178.7; **HRMS** calcd for $C_{21}H_{37}O_6(M^+ - i\text{-Bu})$ 385.2590, found 385.2594; [α] $^{17}_D$ +38.71 (c = 0.72, $CHCl_3$).
8. Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, 93, 5286.
9. Schow, S. R.; McMorris, T.C. *J. Org. Chem.* **1979**, 44, 3760.
10. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, J.; Peterson, *J. Am. Chem. Soc.* **1970**, 92, 741.
11. Becker, K. B. *Tetrahedron* **1980**, 36, 1717.
12. Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, 88, 5654.
13. We thank Drs. B. B. Snider (Brandeis University) and F. Koehn (Harbor Branch Oceanographic Institute) for copies of reference spectra of (-)-reiswigin A (**1**).
14. The synthesis was executed as described in order to unambiguously determine the stereoselectivity of the key intramolecular ester enolate alkylation step, although the total number of steps could be reduced in practice to twelve as shown in the following scheme. Selective mono-tosylation of diol **8a**, followed by Johnson orthoester Claisen rearrangement on the resulting monotosylate, directly produced cyclization substrate **18.** However, cyclization of **18** with KHMDS was accompanied by deprotonation at the allyl ether moiety of the side chain appendage which is of no consequence in the synthesis except being a nuisance in characterization of the products. Full details will be described in due course.



18

15. Rios, T.; Quijano, L. *Tetrahedron Lett.* **1969**, 1371.
16. Rios, T.; Gomez, F. *Tetrahedron Lett.* **1969**, 2929.

(*Received in Japan* 27 *May* 1994)