Pergamon

Tetrahedron Letters 39 (1998) 659–662

TETRAHEDRON LETTERS

Stereoselective Synthesis of Highly Substituted and Oxygenated *cis*-Decalins

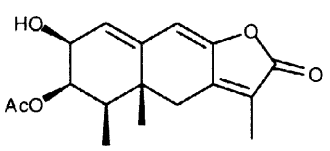
Po-Yi Hsu, Yen-Chun Lee and Chun-Chen Liao*

Department of Chemistry, National Tsing Hua University
Hsinchu, Taiwan 30043

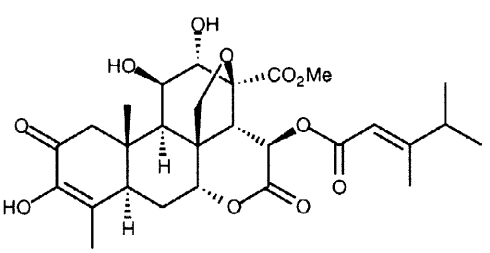
Received 21 October 1997; accepted 21 November 1997

Abstract: Efficient and stereocontrolled four-step preparations of highly substituted and oxygenated *cis*-decalins from commercially available catechol derivatives and various dienophiles.

Stereoselective synthesis of decalins, that are either highly oxygenated or with sufficient provision to oxygenate, is of utmost importance since such structural units are invaluable in the synthesis of natural products with biological importance. The structural complexity of some of the recently isolated natural products [*e.g.* (-)-PF1092A[1] and Bruceantin[2]] demands new and efficient methods. For this reason, development of new methods for the synthesis of stereochemically well defined decalins has become an area of active research as evidenced by recent reports.[3-11] Many organic reactions such as Robinson annulation, Diels-Alder reaction, oxy-Cope and anionic oxy-Cope rearrangements have been commonly employed for the syntheses of the decalin skeletons, but the Cope rearrangement is not quite often used, due to its reversibility and relatively harsh reaction conditions required for it. Here, we report a stereocontrolled synthesis of highly substituted and oxygenated decalins *via* Cope rearrangement of vinylbicyclo[2.2.2]octenones.



(-)-PF1092A



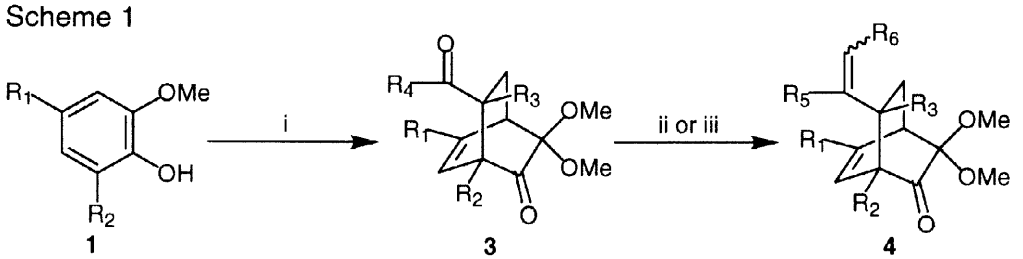
Bruceantin

The bicyclo[2.2.2]octenone **3a** was prepared by the Diels-Alder reaction of ethyl vinyl ketone **2a** with masked *o*-benzoquione generated *in situ* by the oxidation of 2-methoxyphenol **1a** with iodobenzene diacetate. The **3a** was converted into silyl enol ether **4a** which upon heating for 48 h in mestiylene at 220 °C underwent Cope rearrangement smoothly to provide compound **5a** in 70% yield (Scheme 1 and 2). It is understood that the initially formed Cope product of the type **6** isomerized to **5a**. Although 5-silyloxy-1,5-dienes prepared from 5-oxo-1-alkene are known to undergo Cope rearrangement,[12] this is the first example with regard to vinylbicyclo[2.2.2]octenone. We believe that compound **5a** could be transformed into Petasin[13] and related

0040-4039/98/$19.00
PII: S0040-4039(97)10711-0

compounds. In order to find out the generality of this reaction we extended this strategy to compounds **3b**, **3e** and **3h** whose syntheses were reported by us previously.[14] Compounds **3b**, **3e** and **3h** were converted to silyl enol ethers **4b**, **4e** and **4h** which were subjected to Cope rearrangement in presence of trimethyl orthoformate which helps in removing the trace of water to obtain decalins **5b**, **6e** and **6h** in very high yields (Table I).

Scheme 1



i) **2** , IBD, MeOH. ii) TMSOTf, NEt_3. iii) *n*-BuLi, CH_3PPh_3Br, THF.

For **1** **a**: R_1=Me, R_2=H
b: R_1=CO_2Me, R_2=H
c: R_1=CO_2Me, R_2=OMe

For **2**  **a**: R_3=H, R_4=Et
b: R_3=H, R_4=Me
c: R_3=H, R_4=H
d: R_3=Me, R_4=H

For **3** **a**: R_1=Me, R_2=H, R_3=H, R_4=Et
b: R_1=Me, R_2=H, R_3=H, R_4=Me
c: R_1=Me, R_2=H, R_3=H, R_4=H
d: R_1=Me, R_2=H, R_3=Me, R_4=H
e: R_1=CO_2Me, R_2=H, R_3=H, R_4=Me
f: R_1=CO_2Me, R_2=H, R_3=H,R_4=H
g: R_1=CO_2Me, R_2=H, R_3=Me, R_4=H
h: R_1=CO_2Me, R_2=OMe, R_3=H, R_4=Me
i: R_1=CO_2Me, R_2=OMe, R_3=H, R_4=H
j: R_1=CO_2Me, R_2=OMe, R_3=Me, R_4=H

For **4** **a**: R_1=Me, R_2=H, R_3=H, R_5=OTMS, R_6=Me
b: R_1=Me, R_2=H, R_3=H,R_5=OTMS, R_6=H
c: R_1=Me, R_2=H, R_3=H, R_5=H, R_6=H
d: R_1=Me, R_2=H, R_3=Me,R_5=H, R_6=H
e: R_1=CO_2Me, R_2=H, R_3=H,R_5=OTMS, R_6=H
f: R_1=CO_2Me, R_2=H, R_3=H, R_5=H, R_6=H
g: R_1=CO_2Me, R_2=H, R_3=Me,R_5=H, R_6=H
h: R_1=CO_2Me, R_2=OMe, R_3=H, R_5=OTMS, R_6=H
i: R_1=CO_2Me, R_2=OMe, R_3=H, R_5=H, R_6=H
j: R_1=CO_2Me, R_2=OMe, R_3=Me, R_5=H, R_6=H

Vinylbicyclo[2.2.2]octenes are generally converted into *cis*-decalins *via* oxy-Cope or anionic oxy-Cope rearrangements.[15] Cope rearrangement of simple vinylbicyclo[2.2.2]octenes requires high temperatures (>300 °C).[16] If simple vinylbicyclo[2.2.2]octenones can undergo Cope rearrangement smoothly at lower temperatures, it will result in the production of highly substituted and appropriately oxygenated decalins and will greatly increase the scope of the methodology in discussion. Accordingly, the required vinylbicyclo[2.2.2]octenones **4c**, **4d**, **4f**, **4g**, **4i** and **4j** were planned to be prepared from the corresponding formylbicyclo[2.2.2]octenones **3** *via* Wittig olefination. We anticipated that compounds **3c**, **3d**, **3f**, **3g**, **3i** and **3j** could be prepared according to the standard procedure using α,β-unsaturated aldehydes such as acrolein and methacrolein as dienophiles in the Diels-Alder reactions with masked *o*-benzoquinones.

Accordingly, we carried out the reaction between acrolein and masked *o*-benzoquione generated from phenol **1a** under usual conditions. The yield of the formylbicyclo[2.2.2]octenone **3c** was very low and unoxidized phenol always remained. We reasoned that the result may be due to undesired side reaction of IBD with acrolein which we were not able to identify yet. Then, instead of adding 2-methoxyphenol **1a** to the mixture of IBD and acrolein,[14] we added IBD in methanol to the mixture of **1a** and acolein in methanol using a syringe pump during 4 h. The yield of the desired product **3c** has been increased dramatically. Thus present

procedure was adapted for reactions of both acrolein and methacrolein with all 2-methoxyphenols used. Then the formylbicyclo[2.2.2]octenones **3c**, **3d**, **3f**, **3g**, **3i** and **3j** were converted into the corresponding vinylbicyclo[2.2.2]octenones **4c**, **4d**, **4f**, **4g**, **4i** and **4j** in moderate to good yields by Wittig reaction under standard conditions (Scheme 1, Table I). These vinylbicyclo[2.2.2]octenones underwent Cope rearrangement very smoothly at 250 °C to provide *cis*-decalins **6c**, **6d**, **6f**, **6g**, **6i** and **6j** respectively in very high yields (Scheme2, Table I). The stereochemistry of **4c** was established by NOE studies. The stereochemisty of other compounds were predicted by analogy. All the new compounds were characterized by ir, ^{1}H, ^{13}C nmr and mass spectral analyses.

Scheme 2

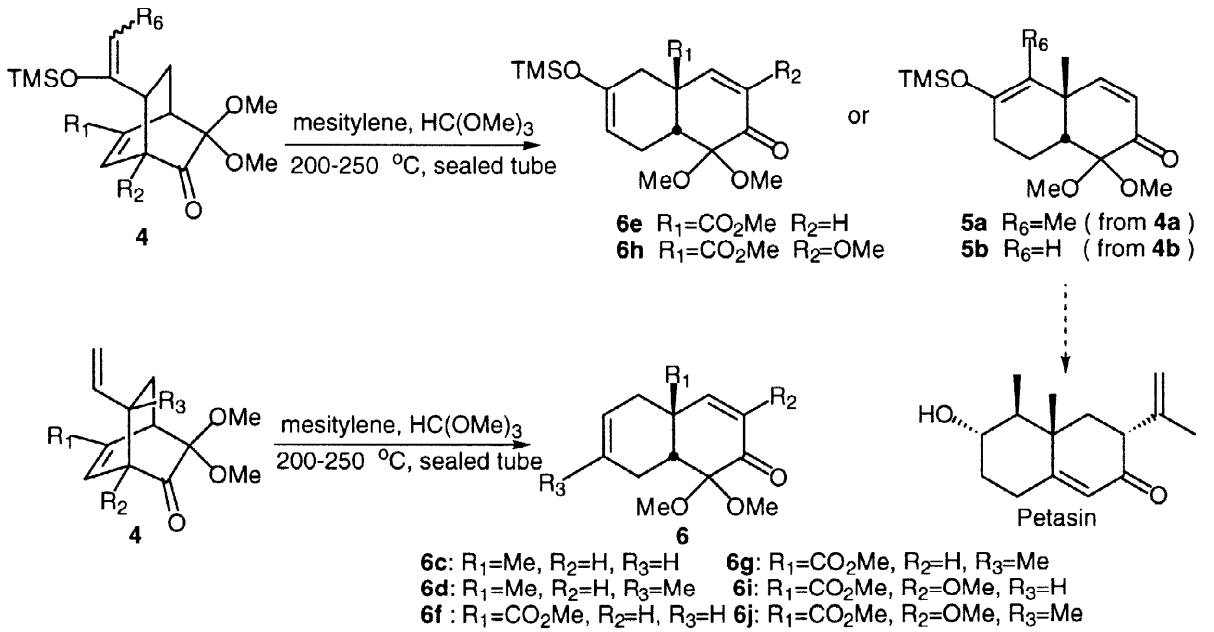


Table I. Preparation of highly substituted and oxygenated *cis*-decalins

Entry	2-Methoxy-phenol	Dienophile	Yield(%) of **3**	Yield(%) of **4**	Cope rearrangement of **4**		
					Temp. (°C)	Time (h)	Yield(%)
1	**1a**	**2a**	**3a** / 88	**4a** / 88	220	48	**5a** / 70
2		**2b**	**3b** / 80	**4b** / 85	250	8	**5b** / 93
3		**2c**	**3c** / 85	**4c** / 65	250	8	**6c** / 88
4		**2d**	**3d** / 80	**4d** / 75	250	8	**6d** / 93
5	**1b**	**2b**	**3e** / 86	**4e** / 90	250	8	**6e** / 95
6		**2c**	**3f** / 80	**4f** / 50	250	10	**6f** / 86
7		**2d**	**3g** / 81	**4g** / 62	250	10	**6g** / 85
8	**1c**	**2b**	**3h** / 89	**4h** / 86	200	8	**6h** / 97
9		**2c**	**3i** / 87	**4i** / 45	250	10	**6i** / 78
10		**2d**	**3j** / 72	**4j** / 52	250	10	**6j** / 80

In conclusion, we have developed an efficient and stereocontrolled four-step preparation of highly oxygenated *cis*-decalins from commercially available catechol derivatives. To the best of our knowledge, we are the first to employ bicyclo[2.2.2]octenones with 2-silyloxy-1,5-diene unit as substrate for Cope rearrangement.

Acknowledgment:

We thank National Science Council (NSC) of Taiwan, R.O.C. for financial support and Dr. P. Dharma Rao for helpful discussions.

References

1. Tatsuta, K.; Yasuda, S.; Kurihara, K.-I.; Tanabe, K.; Shinei, R.; Okonogi, T. *Tetrahedron Lett.* **1997**, *38*, 1439-1442.
2. Fuchs, P. L.; Chiu, K.-F.; Govindan S. V. *J. Org. Chem.* **1994**, *29*, 311-323.
3. Jackson, W. P.; Ley, S. V. *J. Chem. Soc., Perkin Trans. I* **1981**, 1516-1519.
4. Lavallee, J. F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6033-6036.
5. Liu, H.-J.; Hen, Y. *Tetrahedron Lett.* **1993**, *34*, 423-426.
6. Muller, G.; Jas, G. *Tetrahedron Lett.* **1992**, *33*, 4417-4420.
7. Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589-2592.
8. Bouchard, H.; Lallemand, J. Y. *Tetrahedron Lett.* **1990**, *31*, 5151-5152.
9. Chan, T.-H.; Pereira, O. Z. *J. Org. Chem.* **1994**, *59*, 6710-6716.
10. Lee, T.-H.; Liao, C.-C.; Liu, W.-C. *Tetrahedron Lett.* **1996**, *36*, 5897-5900.
11. Hsu, P.-Y.; Liao, C.-C.; *J. Chem. Soc., Chem. Commun.* **1997**, 1084-1085.
12. Wender, P. A.; Brighty, K. *Tetrahedron Lett.* **1988**, *29*, 6741-6744.
13. Bestmann, H. J.; Witshel, M. C. *Synthesis* **1997**, 107-112.
14. Chu, C.-S.; Lee, T.-H.; Liao, C.-C. *Synlett* **1994**, 635-636.
15. Richard, K. H. in *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5, Chap. 7.
16. Berson, J. A.; Walsh, E. J. *J. Am. Chem. Soc.* **1968**, *90*, 4730-4732.