A MICROWAVE-ACCELERATED INTRAMOLECULAR DIELS-ALDER REACTION APPROACH TO COMPACTIN

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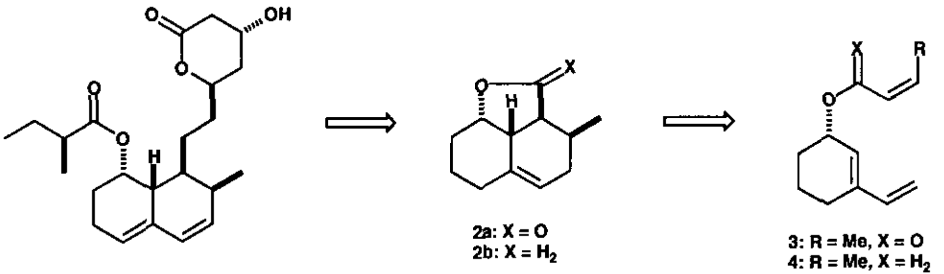
Abstract- Microwave irradiation drastically accelerated the intramolecular Diels-Alder reactions of **5a-c** as compared with conventional heating. The resulting carboxylic acid (**7c**) was converted to the decalin unit (**2a**), which is a possible key intermediate for synthesis of compactin (**1**).

Compactin (**1**), isolated from culture broth of *Penicillium citrinum* and *P. brevicompactum* in 1976 by Endo *et al.*[1a-c] and Brown *et al.*,[1d] respectively, is potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co A) reductase and acts as an effective hypocholesterolemic agent in man. Numerous synthetic approaches have been reported.[2,3] One of the most efficient approaches to the decalin unit (**2a**) would seem to be synthesis from **3** (Figure 1). Similar approaches were proposed by Funk *et al.*[3a] and Hecker and



1

2a: X = O
2b: X = H_2

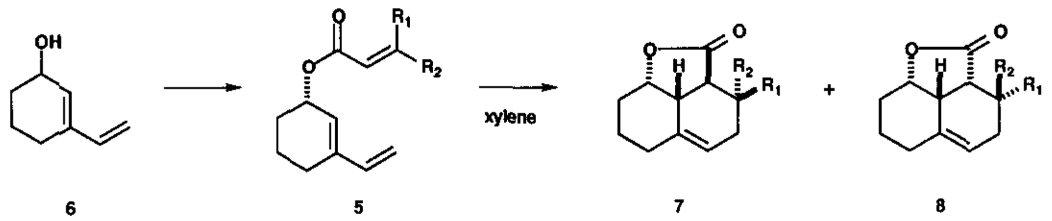
3: R = Me, X = O
4: R = Me, X = H_2
5: R = CO_2R', X = O

Figure 1

Heathcock,[3b] but without success. Funk *et al.* reported intramolecular Diels-Alder reaction of **4** with *exo* cycloaddition, but the stereoselectivity was low (*exo* : *endo* = 4 : 1).[3a] In this paper, we describe intramolecular Diels-Alder reaction of **5**, which has a carboxyl group instead of the methyl group in **3** for the activation of the dienophile.

Substrates (**5a-c**) for the Diels-Alder reaction were prepared from 3-ethoxy-2-cyclohexenone.[4] Addition of vinylmagnesium bromide to 3-ethoxy-2-cyclohexenone followed by treatment with HCl, then reduction with $LiAlH_4$ gave **6** in 71% yield. Esterification of **6** was performed by using the Mitsunobu reaction[5] with ethyl hydrogen malate and ethyl hydrogen fumarate[6] to give **5a** and **5b** in 68% and 33% yields, respectively.[7] The carboxylic acid (**5c**) was also prepared by acylation of **6** with BuLi and maleic anhydride in 83% yield.[7]

Intramolecular Diels-Alder reaction of **5a** was carried out by heating at 130 °C for 10 h in *o*-xylene (Figure 2). The desired *exo* adduct (**7a**) was obtained with high stereoselectivity, and the *endo* adduct (**8a**) and another diastereomer (**8b**) were also formed.[8] The formation of **8b** was considered to occur by isomerization from **7a**, and not from in the reaction of **5b** after isomerization of **5a**. The Diels-Alder reaction of **5b** afforded the another diastereomer (**7b**) as the *exo* adduct with high selectivity. Further, heating of **7a** in *o*-xylene resulted in isomerization to **8b**. The formation of isomers other than *exo* and *endo* adducts has been



a: $R_1 = CO_2Et$, $R_2 = H$
b: $R_1 = H$, $R_2 = CO_2Et$

c: $R_1 = CO_2H$, $R_2 = H$
d: $R_1 = H$, $R_2 = CO_2H$

Results of the Intramolecular Diels-Alder Reaction

substrate	condition	time	yield (%)	products
5a	130 °C	10 h	63	7a : 8a : 8b = 91 : 8 : 1
5a	microwave	9 min X 2	54	7a : 8a : 8b = 94 : 5 : 1
5b	130 °C	10 h	76	7b : 8b = 87 : 13[a)]
5c	130 °C	10 h	51	7c : 8c : 8d = 82 : 6 : 12
5c	microwave	9 min X 5	52	7c : 8c : 8d = 85 : 6 : 9

a) Another isomer was not detected.

Figure 2

reported by Jenkins *et al.*[9a] and Ziegler *et al.*[9b] in intramolecular Diels-Alder reactions of similar systems. The reaction of the carboxylic acid (**5c**) also gave the *exo* adduct (**7c**) as the major product, and the ratio of **8d** was increased. However the *endo*/*exo* ratio was similar to that of the reaction of **5a** because **8d** was generated by isomerization from the *exo* adduct (**7c**). Next, microwave irradiation was employed. Heating with microwave irradiation is known to accelerate various reactions; the temperature of the solvents is drastically increased.[10] The malate (**5a**) was irradiated with microwaves twice for 9 min each in order to keep the temperature below 130 °C in an open vessel by using a domestic microwave oven (Sharp Hi-Cooker RE-110, 2450 MHz, 500 W). The reaction was drastically accelerated. The carboxylic acid (**5c**) was similarly irradiated five times for 9 min to give the *exo* adduct (**7c**) as the major product.

The resulting **7c**, having the required stereochemistry, was converted to **2a** as follows (Figure 3). Selective reduction (DMF, oxalyl chloride, $NaBH_4$)[11] of the carboxyl group in **7c** gave the alcohol **9a** in 64% yield. Mesylation of the alcohol followed by treatment with NaI gave **9b** in 48% yield. Finally, reduction of the iodide (**9b**) (Bu_3SnH, AIBN) gave the decalin unit (**2a**)[12] in 86% yield.

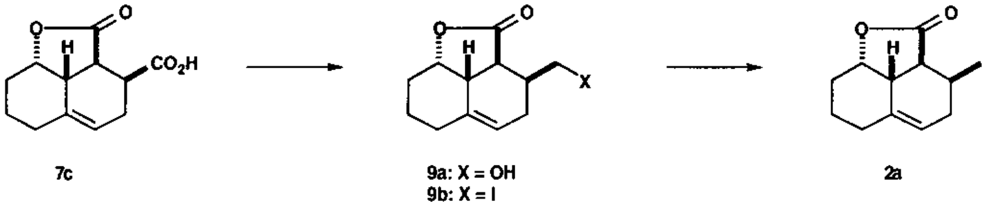


Figure 3

Thus, an effective synthesis of the decalin unit (**2a**) required for an approach to compactin (**1**) was accomplished by using microwave-accelerated intramolecular Diels-Alder reaction of **5c**.

REFERENCES AND NOTES

1. (a) A. Endo, M. Kuroda, and Y. Tsujita, *J. Antibiot.*, 1976, **29**, 1346; (b) A. Endo, M. Kuroda, and K. Tanzawa, *FEBS Lett.*, 1976, **72**, 323; (c) A. Endo, Y. Tsujita, M. Kuroda, and K. Tanzawa, *Eur. J. Biochem.*, 1977, **77**, 31; (d) A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp, and R. H. Thompson, *J. Chem. Soc., Perkin Trans. I*, **1976**, 1165.

2. (a) For a review, see: T. Rosen and C. H. Heathcock, *Tetrahedron*, 1986, **42**, 4909; (b) H. Hagiwara, T. Nakano, M. Kon-no, and H. Uda, *J. Chem. Soc., Perkin Trans. I*, **1995**, 777, and references cited therein.

3. For related Diels-Alder reaction approaches, see: (a) R. L. Funk, C. J. Mossman, and W. E. Zeller, *Tetrahedron Lett.*, 1984, **25**, 1655; (b) S. J. Hecker and C. H. Heathcock, *J. Org. Chem.*, 1985, **50**, 5159; (c) S. Nagashima, T. Taishi, and K. Kanematsu, *Heterocycles*, 1994, **39**, 55; (d) *idem*, *Tetrahedron Lett.*, 1994, **35**, 3577.

4. W. F. Gannon and H. O. House, *Org. Syn., Coll. Vol.*, 1973, **2**, 539.

5. O. Mitsunobu, *Synthesis*, **1981**, 1.

6. S. M. Spatz and H. Stone, *J. Org. Chem.*, 1958, **23**, 1559.

7. *E*/*Z* Isomerization was not observed.

8. The stereochemistry of **7** and **8** was confirmed by ^{1}H-nmr and its n.O.e. experiments.

9. (a) P. R. Jenkins, K. A. Menear, P. Barraclough, and M. S. Nobbs, *J. Chem. Soc., Chem. Commun.*, **1984**, 1423; (b) F. E. Ziegler, B. H. Jaynes, and M. T. Saindane, *Tetrahedron Lett.*, 1985, **26**, 3307; (c) For a related study, see: S. D. Burke, S. M. S. Strickland, and T. H. Powner, *J. Org. Chem.*, 1983, **48**, 454.

10. (a) R. Gedye, F. Smith, K. Westway, H. Ali, L. Baldisera, L. Laberge, and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279; (b) R. J. Giguere, T. L. Bary, S. M. Duncan, and G. Majetich, *ibid.*, 1986, **27**, 4945; (c) S. Takano, A. Kijima, T. Sugihara, S. Satoh, and K. Ogasawara, *Chem. Lett.*, **1989**, 87; (d) A. K. Bose, M. S. Manhas, M. Ghosh, V. S. Raju, K. Tabei, and Z. U.-Lipkowska, *Heterocycles*, 1990, **30**, 741; (e) A. Loupy, A. Petit, M. Ramdani, C. Yvanaeff, M. Majdoub, B. Labiad, and D. Villemin, *Can. J. Chem.*, 1993, **71**, 90; (f) K. D. Raner, C. R. Strauss, R. W. Trainor, and J. S. Thorn, *J. Org. Chem.*, 1995, **60**, 2456, and references cited therein.

11. T. Fujisawa, T. Mori, and T. Sato, *Chem. Lett.*, **1983**, 835.

12. ^{1}H-Nmr ($CDCl_3$, 400 MHz) δ: 1.04 (3H, d, $J = 6.8$ Hz), 1.47 (1H, dq, $J = 6.7$, 12.6 Hz), 1.66 (1H, m), 1.81-1.89 (2H, m), 1.95 (1H, m), 2.23-2.28 (2H, m), 2.46 (1H, dd, $J = 13.9$, 3.9 Hz), 2.48-2.59 (2H, m), 2.96 (1H, m), 4.61 (1H, ddd, $J = 12.6$, 8.3, 4.5 Hz), 5.35 (1H, m). Ir ($CHCl_3$) 2960, 2928, 2855, 1771, 1455, 1319, 1263, 1135, 1014, 993, 909 cm^{-1}. High-resolution ms (m/z): Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1147 (M^+).

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