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A NOVEL SYNTHESIS OF THE BASIC CARBON FRAMEWORK OF FREDERICAMYCIN A. PROMISING ROUTES FOR THE SPIRO CHIRAL CENTER CONSTRUCTION OF THE CD-RING SYSTEM

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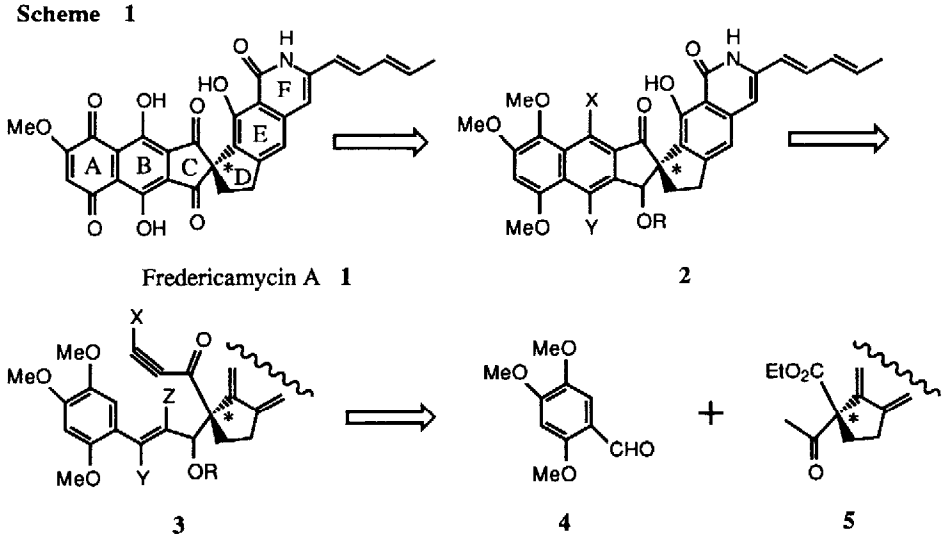
Abstract: The Intramolecular Diels-Alder reactions of the dienynes readily obtainable from the aromatic aldehydes and ethyl 1-acetylcyclopentane-1-carboxylate, were found to proceed in a highly regioselective manner with formation of the novel title compounds as sole products.

Fredericamycin A (**1**) has been distinguished as an unusually attractive target for total synthesis because of its prominent anticancer activity and characteristic spiro structure.[1] While the initial structural elucidation of **1** reported by Pandey *et al.* had only concerned with its relative configuration,[1b] it was recently uncovered that **1** could be produced by *Streptomyces* species in an optically active form.[2] However, the absolute stereochemistry of naturally occurring **1** has not been determined.

Numerous synthetic approaches to **1** have hitherto been reported[3] and Kelly *et al.* has recently completed the first total synthesis of **1** in a racemic modification by employing elegant synthetic methodology.[4] We became interested in the unique structure of **1** involving a single chiral center at the spiro junction of the CD-ring system, and started the program directed at the total synthesis of optically active **1** of definite absolute configuration. However, all the synthetic methods so far developed,[3a-g,i-k,n,p,q,4] turned out to be not applicable to this

Scheme 1

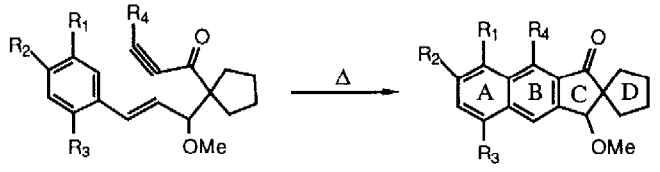


Fredericamycin A **1** **2**

3 **4** **5**

purpose because they have no potential for constructing an asymmetric center at the spiro junction of the CD-ring system in an enantioselective manner.

As a method for preparing **1** in an optically active form, the novel synthetic strategy pictured in **Scheme 1** was designed in which the regioselective intramolecular Diels-Alder reaction is ingeniously employed. Thus, when the intramolecular Diels-Alder reaction of the dienyne (**3**) obtainable from 2,4,5-trimethoxybenzaldehyde (**4**) and the optically active ethyl 1-acethylcyclopentane-1-carboxylate derivative (**5**), undergoes in a highly regioselective manner, the optically active hexacyclic compound (**2**) in which the asymmetric center is involved at the desired position can be produced after concomitant aromatization of the initially formed B-ring. Subsequent chemical manipulations of functionalities can give rise to optically active **1** from **2.** According to this synthetic route, it may be also possible to establish the absolute configuration of naturally occurring **1** by use of optically active **5** of the known absolute stereochemistry.



6 **7**

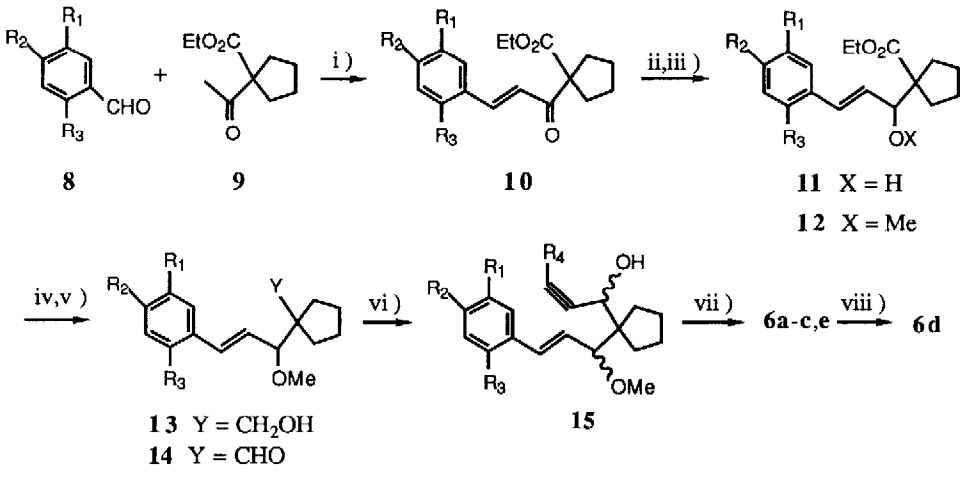
	R_1	R_2	R_3	R_4
a:	H	H	H	TMS
b:	OMe	H	OMe	TMS
c:	OMe	OMe	OMe	TMS
d:	OMe	OMe	OMe	$SiMe_2Ph$
e:	OMe	OMe	OMe	CH_2OTHP

In order to explore feasibility of the designed synthetic strategy, the intramolecular Diels-Alder reactions of the dienynes (**6a-e**), the model compounds of **3**, were first studied. We wish to report here that the intramolecular Diels-Alder reactions of **6b-e** proceed in a highly regioselective manner with exclusive formation of the 2,2-tetramethylene-benz[f]indane derivatives (**7b-e**) corresponding to **2**, as sole products.

The requisite dienynes (**6a-e**) could be readily prepared following the reaction steps shown in **Scheme 2**. Thus, aldol condensations of the aromatic aldehydes (**8a-c**) with ethyl 1-acetylcyclopentane-1-carboxylate (**9**)[5] followed by reductions of the enones (**10a-c**)[6] and methylations of the secondary alcohols (**11a-c**), afforded the methyl ethers (**12a-c**). These were derived to the aldehydes (**14a-c**) by way of the primary alcohols (**13a-c**) by sequential reductions and oxidations. Additions of the lithium acetylides to **14a-c** followed by oxidations gave rise to **6a-c,e**. Exchange of the trimehtylsilyl group of **6c** with a dimethylphenylsilyl group readily produced **6d**.

With **6a-e** in hand, the crucial intramolecular Diels-Alder reaction was first attempted using **6a**. Thus, when a solution of **6a** in o-dichlorobenzene was heated in an evacuated sealed tube, **7a** could be produced in 96% yield after concomitant oxidation of the initial addition product during the addition reaction. Being encouraged by this result, the intramolecular Diels-Alder reactions were next examined employing **6b-e** which bear the aromatic rings substituted with two or three methoxy groups to explore the regioselectivity of addition reaction. As summarized in **Table 1**, the reactions were found to proceed in a highly regioselective manner, affording **7b-e** in good to excellent yields. The structure of **7a-e** could be readily determined by their spectral data.[7]

Scheme 2



8 **9** **10** **11** X = H **12** X = Me

13 Y = CH_2OH **14** Y = CHO **15** **6a-c,e** → **6d**

i) LDA / THF, then **8**, a: 40% ; b: 81% ; c: 74%. ii) $NaBH_4$-$CeCl_3$·$7H_2O$ / MeOH for **10a,c** , DIBAL-H / for **10b**, a: 95% ; b: 56% ; c: 97%. iii) NaH / DMF, then MeI for **11a,c** , MeI / Ag_2O for **11b**, a: 93% ; b: 69% ; c: 88%. iv) DIBAL-H / THF, a: 99% ; 61% ; c: 93%. v) SO_3-Py / DMSO / Et_3N for **13a,c** , PCC / CH_2Cl_2 for **13b**, a: 95% ; b: 60% ; c: 96%. vii) LiC≡CTMS for **14a-c**, LiC≡CCH_2OTHP / Et_2O for **14e**, a: 98%, b: 82% ; c: 91% ; e: 72%. vii) MnO_2 / Ch_2Cl_2 for **15a,c,e**, PCC / CH_2Cl_2 for **15b**, a: 96% ; b: 66% ; c: 77% ; e: 87%, viii) (1) $^nBu_4NF$ / THF (2) ^{n}BuLi / THF, then $Me_2PhSiCl$ for **6c** : 43%.

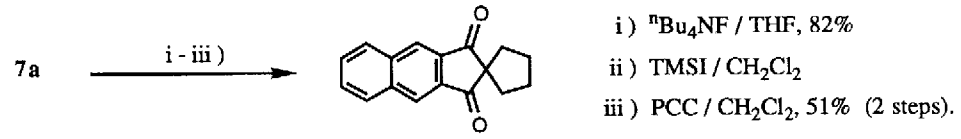
Table 1 Results of the Intramolecular Diels-Alder Reactions of the Dienynes (**6a-e**)[a)]

Run	6	Reaction Condition		Yields of 7 (%)
		Temp.(°C)	Time (h)	
1	**a**	200	3	96
2	**b**	170	2	100
3	**c**	180	2	100
4	**d**	200	2	68[b)]
5	**e**	200	2	73[b)]

a) All reactions were carried out in o-dichlorobenzene. b) Not optimized.

In order to firmly establish the assigned structures of **7a-e**, the simplest addition product (**7a**) was derived to known 2,2-tetramethylene-benz[f]indane-1,3-dione (**16**) previously synthesized by Bach *et al.*[3g)] As shown in **Scheme 3**, desilylation of **7a** followed by cleavage of the methyl ether[8)] and oxidation of the resulting secondary alcohol, smoothly produced **16**, mp. 131-132°C. The dione (**16**) was rigorously identified with an authentic sample, mp 128 - 129°C, by measuring the mixed melting point, mmp 130 - 131°C and comparing their

Scheme 3



16

spectral data.

As described above, the intramolecular Diels-Alder reactions of **6b-e** was found to proceed in a highly regioselective manner to afford good to excellent yields of **7b-e**. Application of this novel methodology to the synthesis of optically active **1** of the definite absolute configuration is in progress.

Acknowledgement: The authors are indebted to Professor R. D. Bach, Wayne State University, for providing us with an authentic sample of **16** and copies of its ^{1}H- and ^{13} C-NMR spectra.

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7) Representative IR and ^{1}H-NMR data of **7a-e** are as follows. **7a:** IR ($CHCl_3$) 1715 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 0.52 (9H, s, $SiMe_3$), 1.68-2.19 (8H, m, aliphatic H), 3.48 (3H, s, OMe), 4.59 (1H, s, CHOMe), 7.42-8.57 (5H, m, aromatic H). **7b:** ^{1}H-NMR ($CDCl_3$) 0.29 (9H, s, $SiMe_3$), 1.35-2.43 (8H, m, aliphatic H), 3.43 (3H, s, CHOMe), 3.85 and 3.98 (each 3H, each s, OMe x 2), 4.57 (1H, s, CHOMe), 6.69 and 6.86 (each 1H, each d, J 9.0 Hz, aromatic H x 2), 8.38 (1H, s, aromatic H). **7c:** ^{1}H-NMR ($CDCl_3$) 0.31 (9H, s, $SiMe_3$), 1.58-2.20 (8H, m, aliphatic H), 3.44 (3H, s, CHOMe), 3.61, 4.02 and 4.06 (each 3H, each s, OMe x 3), 4.54 (1H, s, CHOMe), 6.73 and 8.32 (each 1H, each s, aromatic H x 2). **7d:** ^{1}H-NMR ($CDCl_3$) 0.51 and 0.53 (each 3H, each s, Me x 2),1.40-2.22 (8H, m, aliphatic H), 3.20 (3H, s, CHOMe), 3.45, 3.89 and 4.01 (each 3H, each s, OMe x 3), 4.52 (1H, s, CHOMe), 6.70 (1H, s, aromatic H), 7.13-7.69 (5H, m, aromatic H), 8.37 (1H, s, aromatic H). **7e:** ^{1}H-NMR ($CDCl_3$) 1.14-2.21 (14H, m, aliphatic H), 3.43 and 3.44 (each 1.5H, each s, OMe), 3.92 (3H, s, OMe), 4.01 (6H, s, OMe x 2), 4.48(1H, s, CHOMe), 4.92-5.08 (1H, m, -OCHO-), 5.47 and 5.97 (each 1H, each dd, J 9.0 and 12.0 Hz, $ArCH_2O$-), 6.80 and 8.40 (each 1H, each s, aromatic H).
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