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Stereocontrolled [3 + 2] Annulations with Arene Chromium Tricarbonyl Complexes: Construction of Spirocyclic Compounds Related to Fredericamycin A

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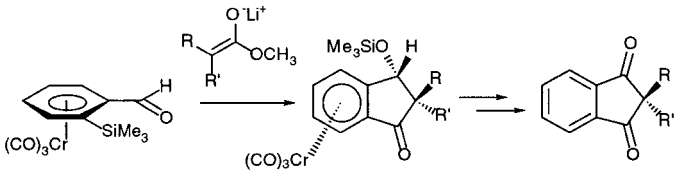
ABSTRACT



An efficient method has been developed for the stereocontrolled construction of polycyclic and spirocyclic compounds, including the spirocyclic core of the antitumor agent fredericamycin A. The strategy involves a one-pot aldol addition/Brook rearrangement/cyclization sequence beginning from arene chromium tricarbonyl complexes and can formally be described as a [3 + 2] annulation.

Fredericamycin A (**1**), which was isolated from *Streptomyces griseus* in 1981,[1] exhibits potent in vitro cytotoxic activity and possesses efficaceous antitumor activity against a variety of tumor models, including P388 leukemia, B16 melanoma, and CD8F mammary.[2] The promising biological profile of **1**, along with the unique and challenging architecture, has motivated considerable effort toward its total synthesis. The spirocyclic core is the synthetically most prominent feature to be addressed, and a variety of novel strategies for its construction have been developed.[3] Although a number of model studies have demonstrated chemically efficient routes to this moiety, the stereoselective synthesis of the quaternary spirocyclic center has proven to be much more challenging. The difficulty of this task is amplified for the construction of fredericamycin A itself, since the asymmetry of the spiro center is due only to the well-separated methoxy functionality of the A ring. Thus, although several total syntheses of fredericamycin A have appeared over the past decade,[4] it was not until recently that an asymmetric synthesis was achieved.[5] Recently we reported an efficient strategy for the stereoselective bis-functionalization of arene chromium tricarbonyl complexes mediated by a Brook rearrangement.[6] As part of our research objective to enhance the synthetic utility of this process, we are currently developing one-pot

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(1) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszaios, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389−1401.

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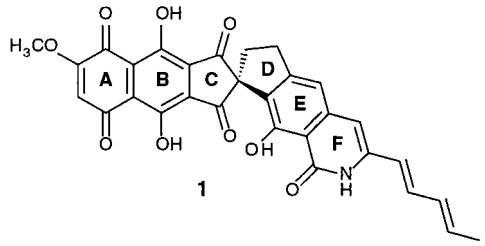
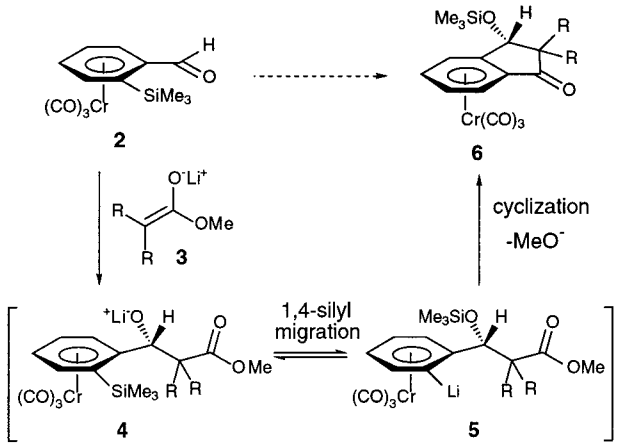


Figure 1. Fredericamycin A.

syntheses of polycyclic and spirocyclic ring systems from arene chromium tricarbonyl precursors. Herein we report the application of this strategy to the stereoselective synthesis of the spirocyclic core of fredericamycin A.

Our strategy, as outlined in Scheme 1, entails addition of lithium ester enolates **3** to arene chromium tricarbonyl

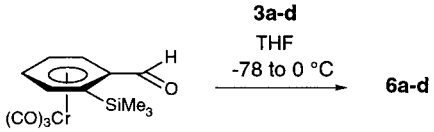
Scheme 1

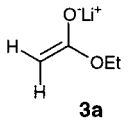
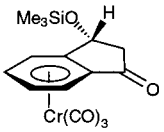
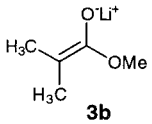
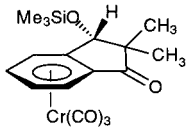
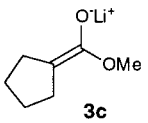
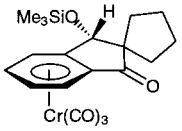
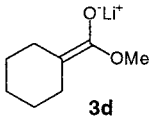
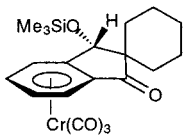


complex **2**. We anticipated that the initial aldol addition would generate a quaternary carbon center and trigger the subsequent 1,4 carbon-to-oxygen silyl migration and cyclization to afford products **6**. The overall transformation can formally be described as a [3 + 2] annulation reaction. Since the products **6** contain planar chirality associated with the chromium arene moiety as well as the newly generated stereogenic center, two diastereomers could potentially be generated when symmetrically substituted ester enolates are employed. In the consideration of this strategy, we were encouraged by related aldol additions of lithium enolates to *ortho*-substituted chromium benzaldehyde complexes reported by Brocard and co-workers, which proceed with complete diastereoselectivity.[7]

Our initial studies with symmetrically substituted ester enolates established that the desired aldol addition/Brook rearrangement/cyclization sequence occurs with very good chemical efficiency and excellent diastereoselectivity (Table 1). The initial aldol reaction was achieved by the addition

Table 1. Annulation Reactions with Symmetrically Substituted Enolates



entry	enolate	product (% yield)
1	 **3a**	 **6a** (20)
2	 **3b**	 **6b** (70)
3	 **3c**	 **6c** (72)
4	 **3d**	 **6d** (84)

of lithium ester enolates **3a**−**d** to racemic arene chromium tricarbonyl complex **2** in THF solution at −78 °C. Warming the reaction flask to ca. −20 °C induced silyl migration and cyclization to provide the corresponding chromium tricarbonyl complexed indanone ring systems **6a**−**d**. Silyl migration could be induced at lower temperatures through the addition of HMPA or other lithium cation chelators to the

(4) (a) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc*. **1988**, *110*, 6471−6480. (b) Rama Rao, A. V.; Singh, A. K.; Rao, B. V.; Reddy, K. M. *Tetrahedron Lett*. **1993**, *34*, 2665−2668. (c) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Chim. Soc. Fr*. **1993**, *130*, 447−449. (d) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc*. **1994**, *116*, 9921−9926. (e) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Am. Chem. Soc*. **1994**, *116*, 11275−11286. (f) Boger, D. L.; Huter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc*. **1995**, *117*, 11839−11849.

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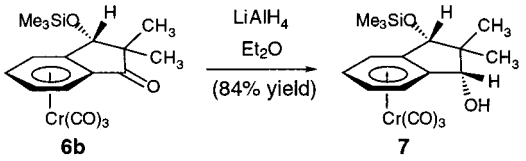
reaction solution.[8] However, these additives also appeared to enhance the reactivity of the lithium alkoxide byproducts, resulting in extensive product decomposition. It is also notable that the disubstituted enolates **3b**−**d** serve as much more efficient reactant partners in this process than unsubstituted enolate **3a**, which afforded only low yields of **6a**.

We were pleased to find in all cases that only a single product diastereomer could be detected by ^{1}H NMR analysis of the crude reaction mixtures. Purification by flash chromatography on silica gel afforded the diastereomerically pure compounds **6a**−**d** as orange-colored solids. Although we were unable to grow crystals of sufficient quality for X-ray analysis, verification of the relative stereochemistry was achieved by reduction of compound **6b** as depicted in Scheme 2. Specifically, addition of $LiAlH_4$ to an Et_2O

Scheme 2



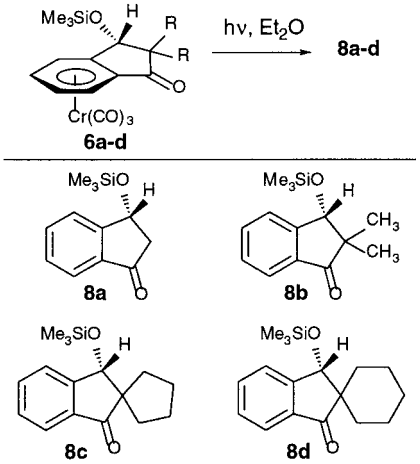
6b **7**

solution of **6b** afforded a single diastereomer of **7**, in which hydride delivery had occurred from the face opposite to the sterically bulky chromium tricarbonyl group. The crystalline product **7** was suitable for X-ray analysis, which verified the proposed structure and established the *cis* relationship between the chromium moiety and the silyl ether functionality generated by the [3 + 2] annulation process.

Since the chromium tricarbonyl group effectively blocks the complexed face of arene complex **2**, the observed stereochemical outcome of the [3 + 2] annulation process is consistent with exclusive *exo* addition of the enolates to the *syn* aldehyde rotamer of **2** depicted in Scheme 1. As originally proposed by Davies and co-workers, selective reaction of this rotameric isomer may result from the ability of the oxophilic silyl group to precoordinate the aldehyde oxygen.[9] The importance of this attractive interaction is further suggested by previously reported aldol additions to *ortho*-substituted chromium benzaldehyde complexes. That is, with *ortho* substituents other than silyl groups,[7] or in the presence of Lewis acidic additives that would competitively chelate the aldehyde carbonyl,[10] the *opposite* relative stereochemistry is observed, consistent with *exo* addition of the nucleophile to the *anti* aldehyde rotamer.

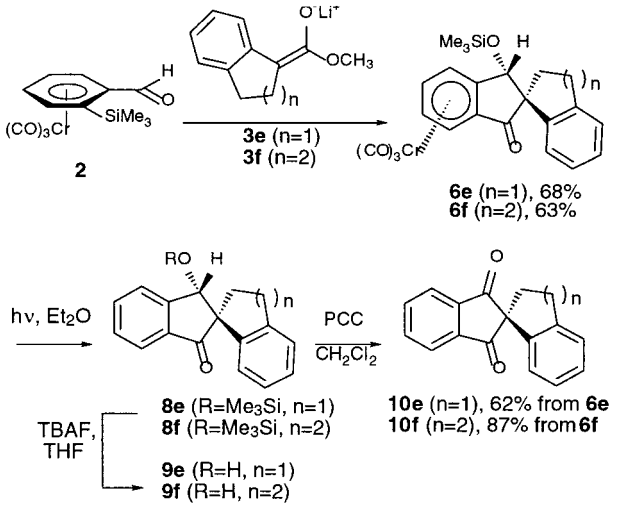
Following these stereochemical studies, we verified that essentially quantitative removal of the chromium fragment was conveniently achieved by exposure to air and sunlight to afford products **8a**−**d** (Scheme 3).

Scheme 3. Removal of $Cr(CO)_3$ Moiety



On the basis of this initial success, we were motivated to attempt the same annulation protocol with unsymmetrically disubstituted ester enolates. In these cases, two new stereogenic centers would be generated in the initial aldol addition, which in conjunction with the planar chirality of the arene chromium tricarbonyl moiety could generate up to four diastereomeric products. The closest precedent that we are aware of for this transformation involves the Lewis acid catalyzed addition of cyclic or acyclic silyl enol ethers to *ortho*-substituted chromium benzaldehyde complexes, as alluded to previously.[10] These reactions are reported to proceed with moderate to high levels of diastereoselectivity with respect to the two newly generated stereogenic centers. However, since the presence of Lewis acids is not compatible with anionic silyl migrations, it was not certain that our approach would allow useful diastereoselectivity to be

Scheme 4. Construction of Spirocyclic Diones



(8) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084.
(9) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393−407.
(10) (a) Mukai, C.; Cho, W. J.; Kim, I. J.; Kido, M.; Hanaoka, M. *Tetrahedron* **1991**, *47*, 3007−3036. (b) Mukai, C.; Miyakawa, M.; Mihara, A.; Hanaoka, M. *J. Org. Chem.* **1992**, *57*, 2034−2040. (c) Mukai, C.; Kim, I. J.; Furu, E.; Hanaoka, M. *Tetrahedron* **1993**, *49*, 8323−8336. (d) Swamy, V. M.; Bhadbhade, M. M.; Puranik, V. G.; Sarkar, A. *Tetrahedron Lett.* **2000**, *41*, 6137−6141.

achieved in the one-pot formation of products bearing stereogenic quaternary and/or spirocyclic carbon centers.

In practice, we were delighted to find that addition of unsymmetrically disubstituted ester enolates **3e,f** to racemic arene complex **2** under our optimized conditions afforded products **6e,f** in good yields as single diastereomers, demonstrating that complete relative stereochemical control had been achieved in the formation of the spirocyclic center (Scheme 4). The stereochemical relationship between the newly generated spirocyclic and carbinol centers was verified by converting **6e** to the previously reported alcohol **9e**.[3i] Finally, both **6e** and **6f** were readily converted to the corresponding spirodiones **10e** and **10f** characteristic of fredericamycin A through the three-step procedure of chromium removal (*hν*, Et_2O), cleavage of the silyl ether (TBAF, THF), and oxidation (PCC, CH_2Cl_2).

In summary, we have developed an efficient [3 + 2] annulation method for the rapid and diastereoselective construction of polycyclic ring systems bearing new quaternary and/or spirocyclic centers from arene chromium tricarbonyl precursors. Since enantiomerically pure arene chromium tricarbonyl complexes are available through a number of established methods, our strategy appears to possess significant potential for the asymmetric synthesis of spirocyclic ring systems, including fredericamycin A.

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Supporting Information Available: Experimental procedures and complete spectral data for compounds **6b**−**f**, **7**, **8a**−**f**, **9e,f**, and **10e,f** and crystal structure data for **7** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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