A Formal Total Synthesis of (+)-Macbecin I

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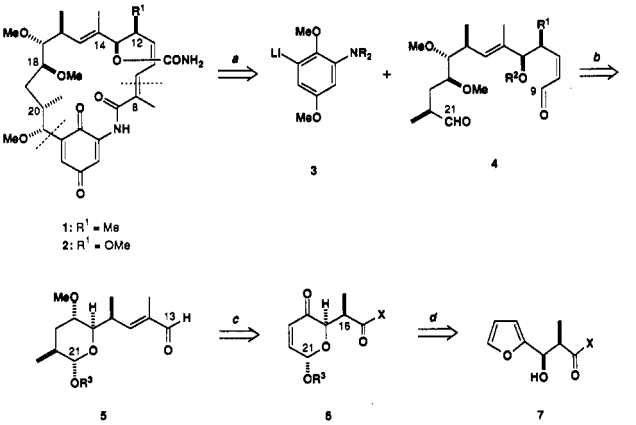
Summary: A 21-step asymmetric synthesis of **23**, which possesses the aryl subunit and the C(9)–C(21) segment of the stereochemically complex ansa chain of (+)-macbecin I (**1**), has been achieved. The subsequent conversion of **23** into **25**, which was an advanced intermediate in Baker's total synthesis of **1**, constitutes a formal synthesis of **1**.

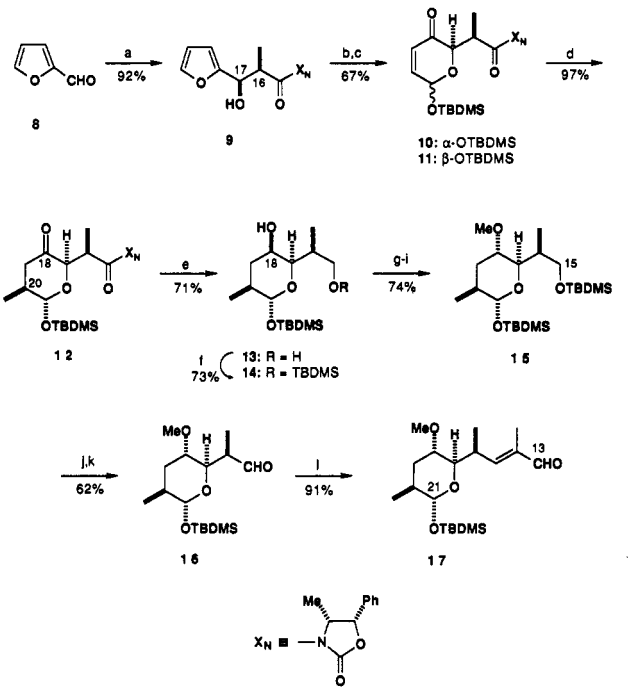
Macbecin I (**1**)[2] and herbimycin A (**2**),[3] which differ only in the nature of the substituent at C(12), are two representative members of the ansamycin family of antibiotics. These macrocyclic lactams exhibit a broad range of biological activities that include antibacterial, antifungal, antiprotozoal, herbicidal, antiangiogenic, antiviral, and antitumor; the anticancer activity of macbecin I is tempered with a remarkably low acute toxicity. These ansamycins are characterized by a 19-membered ring lactam in which the ansa tether bridges the meta positions on a substituted benzoquinone moiety. The ansa chain itself contains seven stereogenic centers, an isolated trisubstituted double bond, and a (*Z*,*E*)-diene. Owing to their inherent structural complexity, **1** and **2** pose significant challenges with respect to both stereochemical control and functional group manipulation and have been targets of a number of synthetic investigations;[4-6] these efforts have recently culminated in the total syntheses of macbecin I (**1**)[5] and herbimycin A (**2**).[6]

In the context of a general program directed toward the synthesis of highly oxygenated natural products, it occurred to us that the furan–hydropyranone oxidative transformation[7] **7** → **6** might be efficaciously exploited in the design of a concise approach to macbecin I and herbimycin A. Toward this end we formulated several distinct strategies, one of which is a linear approach and is outlined in retrosynthetic format in Scheme I. The pairwise dis-

Scheme I



Scheme II[a]



[a] Key: (a) EtCO–X_N, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C; (b) Br_2, MeCN–H_2O, −20 °C; (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (d) Me_2CuLi, TMSCl, THF, −78 °C; H_3O^+; (e) $NaBH_4$, −20 °C; DIBAL-H, 0 °C; (f) TBDMS-Cl, NEt_3, DMAP, CH_2Cl_2, rt; (g) 4-$O_2NC_6H_4CO_2H$, Ph_3P, DEAD, PhH, rt; (h) NaOH, MeOH, rt; (i) KH, MeI, THF, 0 °C; (j) CF_3CO_2H/H_2O (9:1), THF, 0 °C; (k) Pyr-SO_3, NEt_3, DMSO, rt; (l) [2-(triethylsilyl)propionyl]-*N*-cyclohexylimine, *sec*-BuLi, THF −78 to −30 °C; CF_3CO_2H, 0 °C; H_2O.

(1) Recipient of a National Research Service Award from the National Institute of Health.

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(4) For synthetic studies, see: (a) Evans, D. A.; Ornstein, P. L.; Ennis, M. D. 187th National Meeting of the American Chemical Society, St. Louis, April 8–13, 1984, MEDI-154. (b) Evans, D. A. In *Proceedings of the Robert A. Welch Conference on Chemical Research*, Nov 7–9, 1984, Houston, TX, p 13. (c) Baker, R.; Cummings, W. J.; Hayes, J. F.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1237. (d) Burgess, L. E.; Martin, S. F. 196th National Meeting of the American Chemical Society, Los Angeles, Sep 25–30, 1988, ORGN-179. (e) Baker, R.; Castro, J. L.; Swain, C. J. *Tetrahedron Lett.* **1988**, *29*, 2247. (f) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 190. (g) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496.

(5) For an asymmetric total synthesis of (+)-macbecin I, see: (a) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47. For a formal total synthesis of racemic macbecin I, see: (b) Coutts, S. J.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301. Coutts, S. J.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4305.

(6) For an asymmetric total synthesis of herbimycin A, see: Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6015.

(7) For example, see in: (a) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588. (b) Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *Tetrahedron* **1988**, *44*, 3171. (c) Martin, S. F.; Pacofsky, G. J.; Gist, R. P.; Lee, W.-C. *J. Am. Chem. Soc.* **1989**, *111*, 7634. (d) Martin, S. F.; Zinke, P. A. *J. Org. Chem.* **1991**, *56*, 6600.

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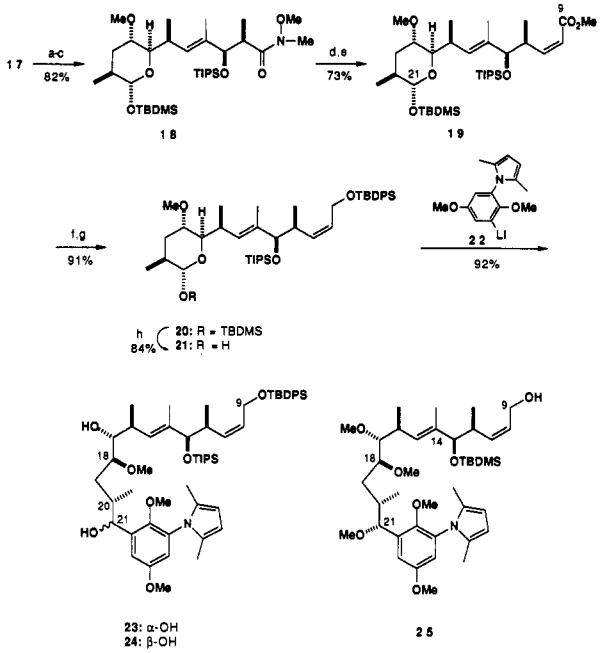
connections *a* lead to consideration of the ansa chain **4** as the key synthetic subgoal. We envisioned that the hydropyran ring in **5** would not only serve as a conformationally biased template for the elaboration of the stereocenters at C(18) and C(20), but it could also be exploited as an advanced synthetic precursor for both macbecin I and herbimycin A. We now communicate our preliminary studies that entail the successful implementation of this strategy for the preparation of **23**, which incorporates C(9)–C(21) of the ansa chain together with the requisite protected aryl subunit of macbecin I. Proof of the relative and absolute stereochemistry of **23** was secured by its conversion to **25**, which was an intermediate in Baker's total synthesis of **1**.[5a]

The absolute stereochemistry at C(16) and C(17) of the ansa chain of macbecin I was set in the opening move of the synthesis by the Evans' asymmetric aldol reaction[8] of furaldehyde (**8**) to give **9** in 92% yield (Scheme II). Oxidative processing of the furan ring followed by protection of the anomeric hydroxyl function as its *tert*-butyldimethylsilyl ether gave a chromatographically separable mixture (3:1) of α- and β-anomers **10** and **11**, respectively.[9] The undesired β-anomer **11** could be readily recycled by sequential deprotection/protection to give **10** in 67% overall yield from **9** after two recycles. Although conjugate addition of lithium dimethylcuprate to enone **10** was not highly stereoselective under standard conditions, the reaction proceeded to give **12** as the exclusive product in 97% yield when conducted in the presence of chlorotrimethylsilane.[10]

At this stage it was necessary to convert the carbonyl group at C(18) into a methyl ether via reduction and subsequent methylation. Unfortunately, stereoselective reduction of the C(18) ketone function to give the requisite equatorial alcohol proved problematic. Extensive model studies employing a wide range of reaction conditions, including various hydride sources as well as equilibrating reduction protocols, invariably produced a preponderance of the unwanted axial stereoisomer. The axial methyl substituent at C(20) appears to play a major role in dictating the facial selectivity in this reduction, even in those cases where reduction was effected under equilibrating conditions. We therefore opted for a stepwise procedure that commenced with hydride reduction of the C(18) ketone in **12**; this reaction proceeded stereoselectively from the equatorial face with concomitant cyclization and loss of the chiral auxiliary to give an intermediate γ-lactone that was further reduced to furnish the diol **13**. Model studies showed that inversion of the stereogenic center at C(18) of **14** to give **15** could be achieved, albeit in modest yield, by a sequence of reactions involving displacement of the corresponding mesylate with cesium propionate[11] followed by hydrolysis and O-methylation. In order to develop a more expedient solution to this problem, we developed a variant of the Mitsunobu reaction[12] that may be employed to effect the stereochemical inversion of hindered secondary alcohols.[13] Thus, **14** was subjected to the Mitsunobu reaction using *p*-nitrobenzoic acid as the nucleophile followed by ester hydrolysis and O-methylation to furnish the ether **15** in 74% overall yield. Selective deprotection of the primary hydroxyl groups at C(15) followed by oxidation using the Parikh protocol[14] provided the aldehyde **16**. The highly stereoselective conversion of **16** into **17** was implemented via Peterson olefination using the anion derived from [2-(triethylsilyl)propionyl]-*N*-cyclohexylimine[15] followed by acid-catalyzed isomerization of the intermediate unsaturated imine prior to its hydrolysis.[15c]

With the key intermediate **17** in hand, it was necessary to decide whether to pursue macbecin I or herbimycin A as the synthetic target, and the former was selected as our initial objective. In the event, subjection of **17** to an Evans' aldol reaction produced an adduct that was transformed into the protected hydroxamate[16] **18** in 82% overall yield (Scheme III). Reduction of the hydroxamate function followed by stereoselective *Z*-olefination according to the Still procedure[17] then gave **19**, which possesses C(9)–C(21) of the ansa chain of macbecin I. In order to set the stage for the addition of the aryl subunit, **19** was first converted into **20** in a straightforward fashion. Selective removal of the TBDMS protecting group from the anomeric center of **20** was achieved using aqueous HF in acetonitrile/THF to give the lactol **21**. The aryl subunit of macbecin I was then introduced by treating **21** with a 3-fold excess of the aryllithium reagent **22**[18,19] to deliver a readily separable

Scheme III[a]



[a] Key: (a) EtCO–X_N, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C; (b) $MeONMeH_2Cl$, $AlMe_3$, CH_2Cl_2, −40 to −10 °C; (c) TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) DIBAL-H, THF, −78 to −50 °C; (e) KHMDS, 18-C-6, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, −78 to −40 °C; (f) DIBAL-H, THF, −20 °C; (g) TBDPS-Cl, DMAP, CH_2Cl_2, rt; (h) 1.5 M aqueous HF, MeCN, THF, rt; (i) **22** (6 molar equiv), TMEDA, Et_2O, −20 °C to rt.

(8) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(9) The structure assigned to each compound was in full accord with its spectral (^1H and ^{13}C NMR, IR and mass) characteristics. Yields cited are for compounds judged to be >95% pure by ^1H NMR. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC, or flash chromatography and gave satisfactory combustion analysis (C, H) and/or identification by high-resolution mass spectrometry.

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(11) Kruizinga, W. H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.

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(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

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mixture (3.5:1) of the adducts **23** and **24** in 92% combined yield. It is interesting to note that **22** added to the C(21) aldehyde function of **21** predominantly via the desired Felkin–Anh (Cram) mode in contrast to that observed in a closely related addition performed by Kallmerten.[5b] The structure of **23** was unequivocally established by its conversion [(a) KH, THF, MeI, 0 °C; (b) TBAF, THF; (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2; (d) TFA, aqueous THF] in 87% overall yield into **25**, which was identical (^1H and ^{13}C NMR) with an authentic sample.[20]

Since **25** was an advanced intermediate in Baker's asymmetric synthesis of macbecin I (**1**),[5a] its preparation by the route outline above constitutes a formal synthesis of **1**. However, we are presently exploring more convergent approaches for the synthesis of **23**, more direct methods for conversion of **23** and related compounds into macbecin I, and several strategies for the total synthesis of herbimycin A from the key intermediate **17**. Moreover, we are examining several stragegies for the total synthesis of herbimycin A from the key intermediate **17**. These results will be revealed in due course.

Acknowledgment. We wish to thank the Robert A. Welch Foundation and the National Institutes of Health (CA 50991) for generous support of this research.

Supplementary Material Available: Complete experimental details for all new compounds (20 pages). Ordering information is given on any current masthead page.

(18) We thank Professor James Kallmerten for providing details for the synthesis of **22**. See also: Guay, V.; Brassard, P. *Heterocyclic Chem.* **1987**, *24*, 1649.

(19) For another account of a similar reaction, see: Plaumann, D. E.; Fitzsimmons, B. J.; Ritchie, B. M.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 941.

(20) We thank Dr. Raymond Baker for providing an authentic sample of **25** for comparison.

Inversion of Configuration in the Displacement of Lithium by Hydrogen during a Transannular 1,4-Hydrogen Transfer Accompanying a [1,2]-Wittig Rearrangement

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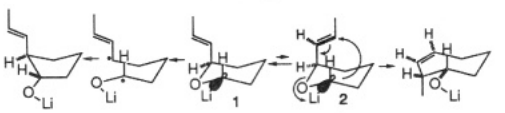
Summary: The presence of a 4-*tert*-butyl group on 2-lithio-6-(*trans*-1-propenyl)tetrahydropyran dramatically changes the rearrangement behavior, inhibiting the formation of [2,3]-Wittig rearrangement product and leading to a 1,4-transannular H-transfer to the lithium-bearing carbon atom with inversion of configuration.

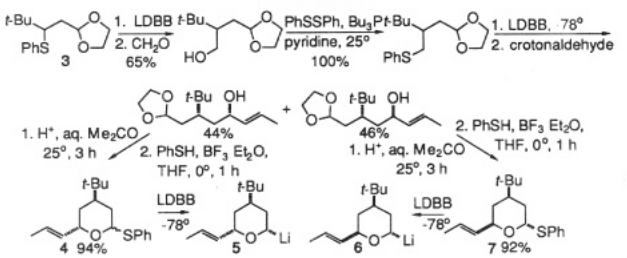
Herein we elucidate the intimate stereochemical course of a rare, if not unique, transannular 1,4-hydrogen transfer that occurs only in the presence of a remote *tert*-butyl group. Recently, we have provided evidence that both the [1,2]- and [2,3]-Wittig rearrangements of **1** occur with inversion of configuration at the lithium-bearing carbon atom by the mechanisms shown in Scheme I.[1] Substrate **1** was generated by reductive lithiation of *trans*-2-(phenylthio)-6-(*trans*-1-propenyl)tetrahydropyran by lithium 4,4′-di-*tert*-butylbiphenylide[2] (LDBB), a reaction the proximate product of which is the other chair conformer of **1** in which the C–Li bond is axial;[3] the rearrangements are believed to require an equatorial C–Li bond which is anti periplanar to the C–O bond that cleaves. The present work was designed to study the rearrangements of **5** and **6** in which stable chair forms containing equatorial C–Li bonds can not be attained.

The syntheses of **5** and **6** are shown in Scheme II.[4,5] Since it has been demonstrated[3] that the proximate product of reductive lithiation of a 2-(phenylthio)tetrahydropyran has an axial C–Li bond, **4** and **7** are expected to yield, respectively, **5** and **6**, the configurations of which

Scheme I

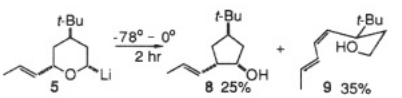


Scheme II



were verified by ^1H NMR spectroscopic examination of the products of quenching with CH_3OD.[3,6]

The results of warming **5** and **6** to 0 °C are shown in eqs 1 and 2.[7] The absence of [2,3]-rearrangement (ring expanded) product from **5** and the trace from **6** are quite significant and in accord with the mechanism in Scheme I. **5** is incapable of attaining a stable conformation



(1)

(possessing an equatorial *tert*-butyl group) in which C2 and C6 are arranged as in **2**, and only one of the stable boat conformations of **6** (along with the related twist confor-

(1) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.*, in press.

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(5) Yields reported in this paper are of isolated and purified material.

(6) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

(7) Other products either remained at the base line during TLC or appeared to be generated during chromatography of the dienes; thus, it is likely that they are polymers or other transformation products of the dienes.

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