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Intramolecular Allenolate Acylations in Studies toward a Synthesis of FR182877

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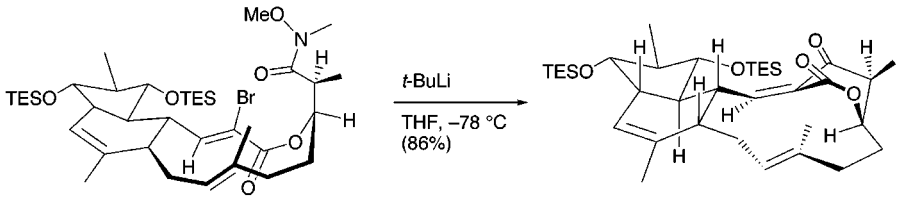
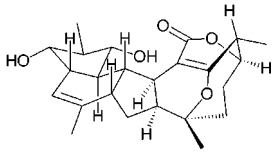
ABSTRACT



During our efforts to synthesize the cytotoxic natural product FR182877, we discovered intramolecular reductive acylations that offer a stereocontrolled alternative to the classical Knoevenagel condensation for the formation of α-alkylidene *β*-keto-*δ*-lactones. Other progress toward a synthesis of FR182877 includes a *π*-allyl Stille coupling and a bromo Horner–Wadsworth–Emmons reaction that forms a 12-membered ring. Structural relationships among FR182877, hexacyclinic acid, macquarimicin A, and cochleamycin A are also discussed.

In a previous publication,[1] we described our biogenetic proposal rationalizing the unique and architecturally complex structure of the cytotoxic natural product FR182877 (**1**), a substance formerly known as WS9885B.[2] We postulated that **1** could have an intrinsic potential for a structural self-assembly from a significantly less complex structure of type **4** (Figure 1) by a cascade of cyclization reactions.[3,4]



1: FR182877 (WS9885B)

Circumstantial support for our biogenetic proposal may be drawn from the close constitutional relationship between **1** and the recently described natural product hexacyclinic acid (**2**).[5] Through isotope incorporation studies, Zeeck and co-workers revealed the polyketide origin of **2** and a pattern of alternating acetate and propionate units that is reflected in compound **4**, a structural type that may be on the biosynthetic pathway leading to FR182877 (**1**).

We also noted that the cyclic alkylidene dicarbonyl of compound **3**, a chemically plausible progenitor of FR182877, is analogous to those found in the cytotoxic natural products macquarimicin A (**5**) and cochleamycin A (**6**).[6] The trans-annular hetero Diels−Alder reaction that could conceivably transform **3** to the full hexacyclic architecture of **1** obscures a biogenetic link that may well exist between FR182877 (**1**) and macquarimicin A (**5**) and cochleamycin A (**6**).

In the course of our efforts to test the chemical basis of the biogenetic hypothesis presented in Figure 1, we observed

(1) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645.

(2) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123. (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204. (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.

(3) Reference 1 details a sequence of type I intramolecular Diels−Alder, ring-closing Knoevenagel and transannular hetero Diels−Alder reactions. We note that an alternative order in which a structure of type **4** undergoes a ring-closing Knoevenagel condensation followed by two sequential transannular Diels−Alder reactions is also appealing from both biogenetic and synthetic standpoints.

(4) For a review of the Diels−Alder reaction in polyketide natural product biosynthesis, see: Ichihara, A.; Oikawa, H. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: New York, 1999; Vol. 5, p 367.

(5) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258.

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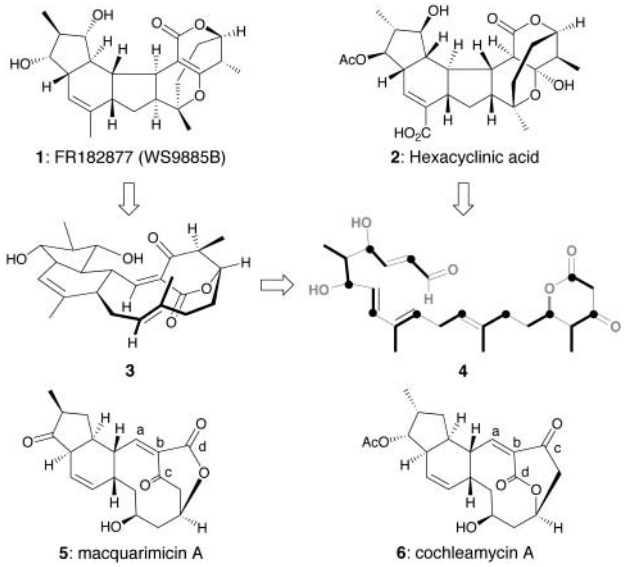
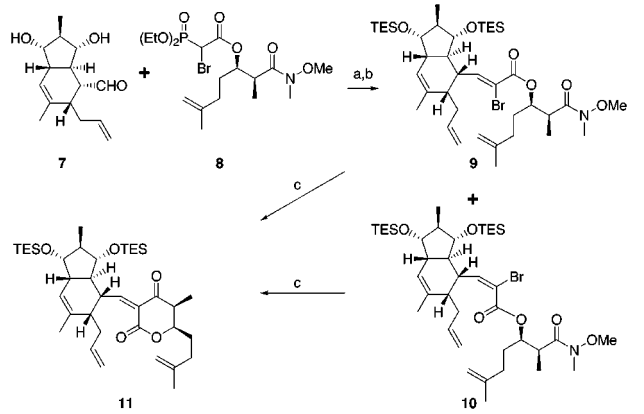


Figure 1. FR182877 and related natural products.

that compounds of type **4** undergo efficient and essentially spontaneous type I intramolecular Diels−Alder reactions[7] in organic and aqueous solvents. Unfortunately, it was not feasible to construct cyclic alkylidene dicarbonyl **3** via an intramolecular Knoevenagel condensation. In the face of this chemical problem, we discovered a facile and useful method for creating geometrically defined alkylidene dicarbonyls analogous to that found in cochleamycin A (**6**). This method, which constitutes an effective alternative to the Knoevenagel process, and our progress toward the goal of achieving a convergent synthesis of FR182877 (**1**) are described in this communication.

As a prelude to an evaluation of a cyclization strategy in which the 12-membered ring of **3** would be fashioned by ring-closing olefin metathesis, hydrindene aldehyde **7** and bromophosphonoacetate **8** were efficiently synthesized and joined through an intermolecular Horner−Wadsworth−Emmons reaction (Scheme 1). This union was particularly smooth using activated[8] $Ba(OH)_2$ in wet THF and afforded a 6.5:1 mixture of isomeric α-bromoenoates that was resolved by SiO_2 chromatography and subsequently converted to compounds **9** and **10** via triethylsilylation of the 1,3-diols. *The apparently unprecedented concept of transforming an α-bromoenoate with a pendant carbonyl electrophile to an α-alkylidene β-keto-δ-lactone through a reductive bond-forming process was our incentive for constructing compounds **9** and **10**.*[9] When a solution of **9** in THF at −78 °C was exposed to *tert*-butyllithium, a rapid cyclization occurred and **11**, the α-alkylidene *β*-keto-*δ*-lactone of unexpected geometry, was isolated in nearly quantitative yield. Interestingly, this facile process is stereoselective but not stereospecific because exposure of the geometrically isomeric α-bromoenoate **10** to the same conditions also results in the formation of compound **11**. This finding is taken as chemical evidence for the intermediacy of a transitory allenolate ion that reacts intramolecularly with the Weinreb amide carbonyl on the side of the small hydrogen substituent[10] to give **11**.[11] Unfortunately, all attempts to correct the geometry of this alkylidene carbonyl by standard isomerization techniques did not succeed.

Scheme 1[a]



[a] Reagents: (a) **8**, Ba(OH)2, THF; then **7**, THF/H_2O, 0 °C. (b) TESCl, Et_3N, DMAP, CH_2Cl_2, 69% over two steps, 6.5:1 *Z/E*. (c) *t*-BuLi, THF, −78 °C, 90−100%.

Having developed an effective Barbier-style *C*-acylation method for creating a needed functional group arrangement, we elected to apply it to a more sophisticated context and turned to the problem of creating compound **19** (Scheme 2). Our hope was that the configuration at C-16 in **19** might favor a reductive cyclization to α-alkylidene *β*-keto-*δ*-lactone **3**,[12] which might then transmute to FR182877 (**1**) through a

(6) (a) Macquarimicin A: Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467. (b) Cochleamycin A: Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244. (c) We believe that the geometry of the alkylidene dicarbonyl moieties of both **5** and **6** are *Z* as depicted in Figure 1 for **6**. This is based on a comparison of their published spectral data: for **5** ($CDCl_3$, *δ*): H_a 6.77 (d, $J = 11.3$ Hz), C_a 154.0, C_b 136.1, C_c 194.2, C_d 165.7. For **6** ($CDCl_3$, *δ*): H_a 6.78 (d, $J = 11.1$ Hz), C_a 155.2, C_b 136.4, C_c 194.2, C_d 165.7. The *Z* geometry of **6** has been determined by a $^{13}C-\{^1H\}$ NOE difference experiment that established the proximity of alkylidene proton H_a and the ketone carbon C_c (reference b). Macquarimicin A (**5**) is nonetheless depicted in Figure 1 as it was originally disclosed.

(7) Roush, W. R. In *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1990; Vol. 2, p 91.

(8) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

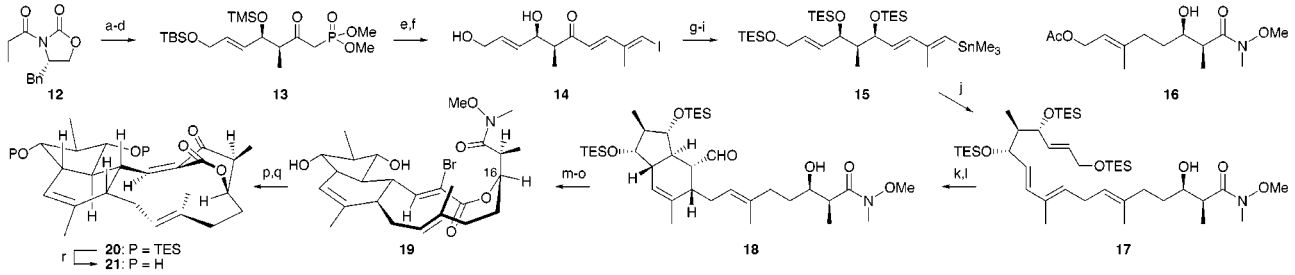
(9) For selected examples of intramolecular acylations of organolithium intermediates, see: (a) Piers, E.; Friesen, R. W. *J. Org. Chem.* **1986**, *51*, 3405. (b) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115. (c) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

(10) For selected studies of allenolates, see: (a) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696. (b) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621. (c) Matsumoto, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1994**, 1211. (d) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051. (e) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230. (f) Ma, D.; Zhu, W. *Org. Lett.* **2001**, ASAP.

(11) Heating of compound **11** in refluxing benzene effected clean and quantitative conversion to a dihydropyran product of an intramolecular hetero Diels−Alder reaction. Whether the ketone or ester carbonyl has participated in the cycloaddition event is as yet unclear; however, this provides a valuable precedent for the final proposed bond-forming event in our synthesis.

(12) Macromodel MM2 calculations predict that the desired *E*-alkylidene **3** is 5.5 kcal/mol more stable than *Z*-alkylidene **21**. It was hoped that the build-up of strain in the transition state for the allenolate acylation may favor a stereospecific acylation to deliver the desired *E*-product.

Scheme 2[a]



[a] Reagents: (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then (*E*)-TBSOCH$_2$CH=CHCHO, −78 → −20 °C. (b) Me_3Al, MeONHMe·HCl, THF, 0 °C, 75% over two steps. (c) TMSCl, imidazole, CH_2Cl_2. (d) $LiCH_2P(O)(OMe)_2$, THF, −78 °C. (e) $Ba(OH)_2$, THF, then (*E*)-*β*-iodomethacrolein, THF/H_2O, 0 °C, 79% over three steps. (f) PPTS, MeOH. (g) Et_2BOMe, $NaBH_4$, THF/MeOH, −78 → 0 °C. (h) TESCl, imidazole, CH_2Cl_2, 86% over three steps. (i) $Me_3SnSnMe_3$, $Pd(Ph_3P)_4$, *i*-Pr_2NEt, PhH, 80 °C, 97%. (j) **16**, Pd_2dba_3, LiCl, *i*-Pr_2NEt, NMP, 40 °C, 86%. (k) TBAF, THF, 0 °C. (l) MnO_2, DMF, 65% over two steps, 1.6:1 ratio of *endo* diastereomers favoring **18**. (m) $(MeO)_2P(O)CHBrCO_2H$, DCC, $NaHCO_3$, CH_2Cl_2, 0 °C. (n) Et_3N•3HF, CH_2Cl_2, 77% over two steps. (o) $Ba(OH)_2$, THF/H_2O, 0 °C. (p) TESCl, imidazole, CH_2Cl_2, 74% over two steps. (q) *t*-BuLi, THF, −78 °C, 86%. (r) PPTS, MeOH, 100%.

transannular hetero Diels−Alder reaction. Evans aldol addition of imide **12**[13] to (*E*)-4-*tert*-butyldimethylsilyloxy-but-2-enal[14] provided a hydroxyimide that was converted to ketophosphonate **13** by Weinreb amide formation, TMS protection,[15] and reaction with dimethyl lithiomethylphosphonate. Diol **14** was obtained via a facile barium hydroxide-mediated Horner−Wadsworth−Emmons reaction with (*E*)-*β*-iodomethacrolein[16] followed by mild hydrolysis of the two silyl ethers. Chelation-controlled ketone reduction[17] gave a *syn*-1,3-diol which was globally protected with chlorotriethylsilane and stannylated[18] to afford dienylstannane **15**. Despite its sensitive nature,[19] stannane **15** underwent a Stille cross-coupling[20] with geranyl acetate-derived building block **16** under ligand-free conditions to give tetraene **17** in 86% yield.[21] Interestingly, MnO_2 oxidation of the primary allylic alcohol produced by a selective deprotection of **17** generated an enal that underwent a spontaneous[22] intramolecular Diels−Alder cycloaddition to a 1.6:1 mixture of endo adducts in favor of **18**.[23]

While the free hydroxyl of **18** is not particularly nucleophilic, it reacted smoothly with bromodimethylphosphonoacetic acid in the presence of DCC. Fluoride-induced cleavage of the triethylsilyl ethers[24] was then followed by an efficient ring-forming Horner−Wadsworth−Emmons condensation mediated by $Ba(OH)_2$ to give the desired tricyclic α-bromo-α,*β*-unsaturated lactone **19** as a single geometrical isomer.[25] When the bis-triethylsilyl ether derived from **19** was exposed to *tert*-butyllithium in THF at −78 °C, an efficient reductive cyclization occurred to afford **20**, the protected geometrical isomer of **3**.[26] Compound **20** is a thermally stable substance that presumably arises via allenolate ion **22** (Figure 2).[27,28] An X-ray crystallographic analysis of diol **21** confirmed this outcome.[29,30]

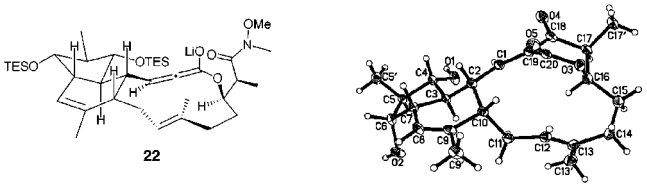


Figure 2. Allenolate intermediate **22** and X-ray structure of α-alkylidene *β*-keto-*δ*-lactone **21**, an isomer of FR182877.

In the course of our ongoing effort to create FR182877 (**1**), a complex, bioactive natural product having a striking

(13) Gage, J. R.; Evans, D. A. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 339.

(14) (a) Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *32*, 6227. (b) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1996**, *61*, 8732.

(15) Reaction of the unprotected hydroxyamide with dimethyl lithiomethylphosphonate generated a diastereomeric mixture of undesired cyclic phosphonates.

(16) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.

(17) (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155. (b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(18) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(19) Though very susceptible to protodestannylation, dienylstannane **15** can be purified by rapid filtration through a short plug of basic alumina. The instability of 2-substituted-1-stannyl-1,3-dienes has been documented. For an example, see: Uenishi, J.; Kawahama, R.; Tanio, A.; Wakabayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1438.

(20) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(21) The stannylation/Stille two-step reaction sequence could be performed on 20 mmol scale.

(22) The corresponding cycloaddition of simple 10-alkyl-2,7,9-decatrienals requires a temperature of 110 °C (see ref 6), suggesting that the substitution pattern of compounds of type **4** favors the pericyclic event. That this cycloaddition occurs spontaneously at ambient temperature is remarkable. At least one example of a room-temperature one-pot MnO_2 oxidation-Diels−Alder reaction has been reported in which manganese byproducts are suspected to have accelerated the cycloaddition; see: Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893. In the present case, we excluded this possibility by isolating the trienal product of the oxidation and observing that cycloaddition still occurs at ambient temperature.

(23) The use of various catalysts, apolar solvents, and/or alternative diol protecting groups shifted the diastereomeric ratio in favor of the undesired *endo* cycloadduct.

(24) Removal of steric crowding in the vicinity of the aldehyde carbonyl was a prerequisite for ring-forming bond constructions.

constitutional resemblance to hexacyclinic acid (**2**) and a potential biogenetic relationship to macquarimicin A (**5**) and cochleamycin A (**6**), we discovered a novel, reductive ring-forming process that is well-suited for stereoselective syntheses of α-alkylidene β-keto-δ-lactones. This method is a stereocontrolled alternative to the traditional Knoevenagel condensation and appears ideally suited to the chemical problems posed by natural products **5** and **6**. We are currently creating contexts in which allenolate behavior may favor a stereocontrolled synthesis of compound **3**.

Acknowledgment. We thank Dr. Raj Chadha for the X-ray crystallographic analysis of **21**. We thank Drs. D. H. Huang and L. B. Pasternack for NMR spectroscopic assistance and Dr. G. Siuzdak for mass spectrometric assistance. Our work was supported by The Skaggs Institute for Chemical Biology at TSRI, NIH/NCI grant CA85526, Merck Research Laboratories, a Beckman Young Investigator Award (E.J.S.), an AstraZeneca Excellence in Chemistry Award (E.J.S.), and predoctoral fellowships from the National Science and Engineering Research Council of Canada (C.D.V.), the National Science Foundation (D.A.V.), and the ACS Division of Organic Chemistry/AstraZeneca Pharmaceuticals (D.A.V.). We also thank Hoffmann-La Roche for a Roche Award for Excellence in Organic Chemistry (C.D.V.).

Supporting Information Available: Characterization data and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) For an example of a $Ba(OH)_2$-mediated macrocyclization, see: Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed*. **2000**, *39*, 4612.

(26) Our preliminary experiments suggest that this reductive acylation method may not be general.

(27) Examination of molecular models suggests that the geometrical requirements for acylation are satisfied only when the allenolate configuration is *S* as shown in **22**.

(28) We were not able to isomerize **20** or **21** to the desired *E* geometry. We could not induce formation of the desired *E*-alkylidene geometry by altering reaction temperature, solvent, and reducing agent.

(29) The synthesis of **21** proceeds in 8.3% yield over 18 steps from **12**, and as such, gram quantities of **21** should be readily available.

(30) The observed trend in the ^{1}H NMR chemical shift of the alkylidene dicarbonyl β-protons correlates well with the expected extent of carbonyl conjugation with the olefin, and with presumed ring strain. In order of predicted increase in ring strain ($CDCl_3$, δ): compound **11**, acyclic: 8.15; compound **20**, 12-membered ring: 7.45; macquarimicin A (**5**), 10-membered ring: 6.77; cochleamycin A (**6**), 10-membered ring: 6.78.