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Development of a Merged Conjugate Addition/Oxidative Coupling Sequence. Application to the Enantioselective Total Synthesis of Metacycloprodigiosin and Prodigiosin R1

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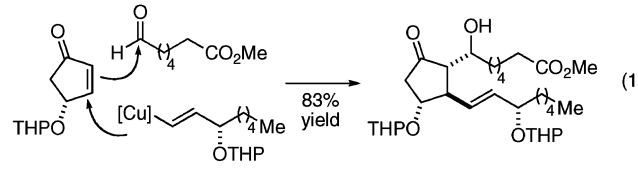
Abstract: A merged conjugate addition/oxidative coupling sequence that represents an efficient strategy for preparing structurally diverse pyrroles has been developed. Success of the method hinged upon the controlled oxidative coupling of unsymmetrical silyl bis-enol ether intermediates, formed by the 1,4-addition of a Grignard reagent with subsequent enolate trapping by a (chloro)silylenol ether. The process was applied to the first enantioselective syntheses of the biologically active pyrrolophane natural products, metacycloprodigiosin and prodigiosin R1.

Introduction

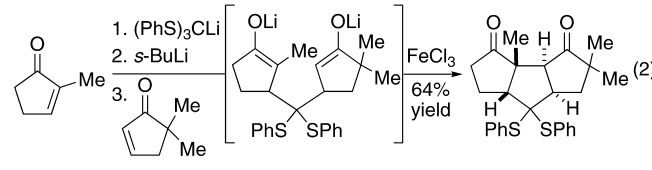
When coupled to multicomponent fragment coupling events, the application of domino transformations can be a powerfully simplifying strategy for the construction of complex molecules.[1] Perhaps the earliest example of this reaction type is seen in Robinson's beautifully direct preparation of tropinone in a single flask from three separate chemical entities.[2] One cornerstone of domino reaction processes is the merged 1,4-addition of a nucleophile to an enone,[3] followed by trapping of the transient enolate with an electrophile. In this manner, three individual components may be coupled in a single operation, as demonstrated elegantly by Noyori and co-workers in their concise prostanoid synthesis (eq 1).[4] While the trapping of enolates formed through conjugate addition with alkyl halides and aldehydes is common, we were interested in merging conjugate additions with oxidative enolate couplings. Such processes have received little attention: to the best of our knowledge, the only reported example of a merged conjugate addition/oxidative coupling sequence is the dithiane linchpin strategy developed by Cohen and co-workers en route to a concise synthesis of hirsutene (eq 2).[5] The lack of further development of this potentially powerful approach to complex structures is most likely due to the inherent difficulties associated with controlling enolate cross-coupling. Despite recent advances in the area of oxidative enolate cross-coupling,[6] there still exists a significant need for general methods that enable access to a diversity of products. For example, controlled ketone−ketone cross-coupling remains a challenge to synthetic methods, yet the products afforded by such a transformation are of great value as precursors to, *inter alia*, furans and pyrroles. The limited progress in this particular area has meant that the oxidative cross-coupling of ketones has not been widely employed in advanced synthetic contexts, which was something we wished to address with our research.

Three-component coupling route to prostanoids:



(1)

Cohen and coworkers merged conjugate addition/oxidative coupling:



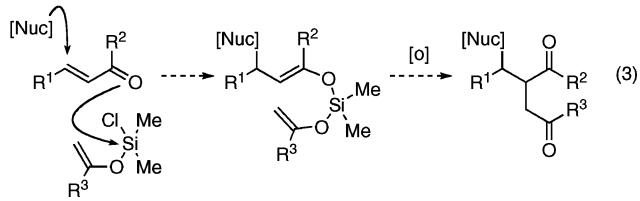
(2)

Silyl bis-enol ethers have been shown to be effective intermediates for selective ketone−ketone cross-coupling,[7] and we wondered whether formation of these species might be achieved by trapping of an enolate generated by conjugate addition to an enone (eq 3). Subsequent oxidation would provide the desired 1,4-diketone derived from the union of three

(1) For a review of domino reactions in organic synthesis, see: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
(2) Robinson, R. *J. Chem. Soc.* **1917**, 762–768.
(3) For a recent review detailing tandem transformations triggered by conjugate additions, see: Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366.
(4) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057–4060.
(5) (a) Ramig, K.; Kuzemko, M. A.; McNamara, K.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1968–1969. (b) Cohen, T.; McNamara, K.; Kuzemko, M. A.; Ramig, K.; Landi, J. J.; Dong, Y. *Tetrahedron* **1993**, *49*, 7931–7942.
(6) For examples of methods for oxidative cross-coupling, see: (a) Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* **1989**, *30*, 3707–3710. (b) Fujii, T.; Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1992**, *33*, 5823–5826. (c) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099–2102. (d) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083–7086. (e) Jang, H. Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005. (f) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585. (g) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560.
(7) (a) Schmittel, M.; Burghart, A.; Malisch, W.; Reising, J.; Sollner, R. *J. Org. Chem.* **1998**, *63*, 396–400. (b) Schmittel, M.; Haeuseler, A. *J. Organomet. Chem.* **2002**, *661*, 169–179. (c) Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667–4669. (d) Avetta, C. T.; Konkol, L. C.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2008**, *10*, 5621–5624.

fragments and provide a useful precursor for natural product synthesis. Successful implementation of this strategy would also provide a general solution to the problem of a merged conjugate addition/oxidative coupling sequence, opening many avenues for the rapid construction of complex molecules.

Proposed merged 1,4-addition/oxidative coupling process:



Specifically, we sought to develop this methodology in the context of the total synthesis of metacycloprodigiosin (**1**)[8] and its recently isolated relative, prodigiosin R1 (**2**).[9] The prodigiosins are a family of brightly colored natural products isolated from Gram-negative bacteria within the *Streptomyces* and *Serriatia* genera.[10] Common to all prodigiosins is the tripyrrole core, with structural variations existing between members depending upon the presence or absence of a medium-sized ring. Of special structural interest are those family members possessing an unusual pyrrolophane core, as exemplified by compounds **1** and **2**. Wasserman and co-workers determined the structure of metacycloprodigiosin (**1**)[8a] and published the first synthesis of it in 1969.[8b] Their approach began with cyclododecanone and afforded the natural product, as a racemate, in 15 steps. Fürster and co-workers reported a 10-step formal synthesis of racemic **1** in 1998.[11] There have been no reported syntheses of prodigiosin R1 (**2**). Due to the range of biological activity displayed by the prodigiosins,[10,12] we wished to develop a *concise and flexible approach that would enable access to enantioenriched material for the first time.* Our strategy would employ a conjugate addition/oxidative coupling sequence followed by a ring-closing metathesis to afford the requisite 12-membered ring (i.e., **3**), which would then be transformed into the respective targets (Scheme 1). Asymmetric induction would be achieved through an enantioselective conjugate addition. Thus, Grignard reagent **5** would be combined with enone **6** and chlorosilane **7** to quickly produce the carbocyclic core of the prodigiosins.

Results and Discussion

Reaction Development. In order to determine the validity of the merged coupling sequence, we initiated a study using enone

Scheme 1. Synthesis Plan for the Prodigiosin Alkaloids

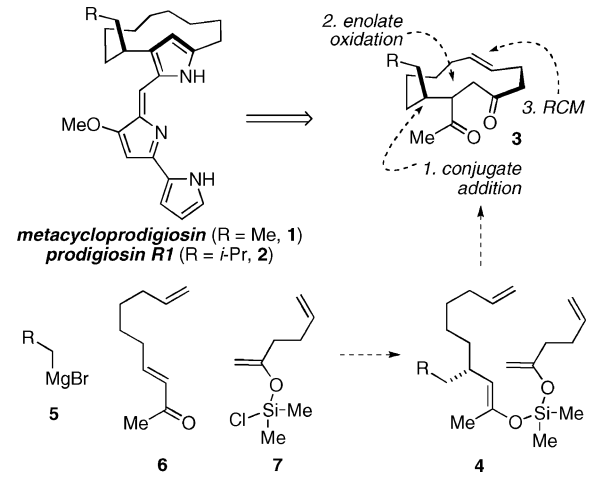
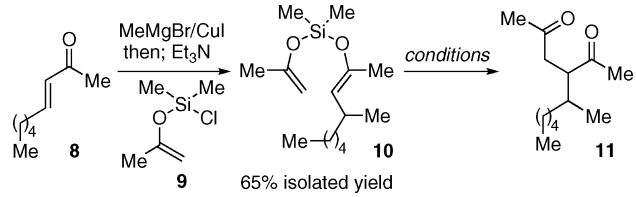


Table 1. Development of Initial Oxidation Conditions



entry	oxidant	solvent	*T* (°C)	yield (%)[a]
1	$CAN/NaHCO_3$	MeCN	0	0
2	$CAN/NaHCO_3$	MeCN	−20	13
3	$Cu(OTf)_2$	MeCN	0	0
4	$V(O)Cl_2(OEt)$	CH_2Cl_2	−78	0
5	Ag_2O	DMSO	23 to 85	0
6	CAN/DTBP	MeCN	−20	50[b]

[a] Isolated yield. [b] Formed as a 1:1 mixture of diastereomers, as determined by ^1H NMR spectroscopy.

8 as the conjugate acceptor (Table 1). A copper(I) iodide-promoted 1,4-addition of methylmagnesium bromide to **8**, followed by the addition of (chloro)silylenol ether **9** (prepared from the corresponding aminosilane, see Supporting Information), proceeded smoothly to afford the requisite silyl bis-enol ether **10** in 65% isolated yield.[13] Cerium(IV) ammonium nitrate (CAN), in conjunction with $NaHCO_3$ as a buffer, has been shown to be an effective reagent for the oxidative coupling of silyl enol ethers[14] and silyl bis-enol ethers.[7] Exposure of **10** to $CAN/NaHCO_3$ in acetonitrile, conditions we had employed successfully in our prior studies into oxidative coupling,[7c,d] provided none of the desired 1,4-diketone **11** (Table 1, entry 1). Instead, only the ketone derived from conjugate addition of the Grignard reagent could be isolated. Cooling the reaction to −20 °C provided some of the diketone, but the maximum yield obtained was only 13% (Table 1, entry 2). We explored a variety of other oxidants reported to couple silyl enol ethers,[15] but these provided none of the desired adduct (Table 1, entries 3−5). Returning to CAN as an oxidant, we replaced $NaHCO_3$ with

(8) (a) Wasserman, H. H.; Rodgers, G. C.; Keith, D. D. *J. Am. Chem. Soc.* **1969**, *91*, 1263–1264. (b) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *J. Am. Chem. Soc.* **1969**, *91*, 1264–1265. (c) Wasserman, H. H.; Keith, D. D.; Rodgers, G. C. *Tetrahedron* **1976**, *32*, 1855–1861. (d) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *Tetrahedron* **1976**, *32*, 1867–1871.

(9) Kawasaki, T.; Sakurai, F.; Hayakawa, Y. *J. Nat. Prod.* **2008**, *71*, 1265–1267.

(10) For reviews of the chemistry and biology of the prodigiosins, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603. (b) Williamson, N. R.; Fineran, P. C.; Leeper, F. J.; Salmond, G. P. C. *Nature Rev. Microbiol.* **2006**, *4*, 887–899. (c) Williamson, N. R.; Fineran, P. C.; Gristwood, T.; Chawrai, S. R.; Leeper, F. J.; Salmond, G. P. C. *Future Microbiol.* **2007**, *2*, 605–618.

(11) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314.

(12) A recent article has described the role of prodigiosin alkaloids in facilitating the exchange of bicarbonate and chloride ions across liposomal membranes: Davis, J. T.; Gale, P. A.; Okunola, O. A.; Prados, P.; Iglesias-Sanchez, J. C.; Torroba, T.; Quesada, R. *Nat. Chem.* **2009**, *1*, 138–144.

(13) Purified on silica gel using EtOAc and hexanes with 5% triethylamine to minimize acid-promoted substrate hydrolysis.

(14) Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* **1989**, *30*, 3707–3710.

(15) (a) Cu(II) triflate: Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, 3741–3742. (b) $VO(OEt)Cl_2$: Fujii, T.; Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1992**, *33*, 5823–5826. (c) Ag_2O: Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 649–651.

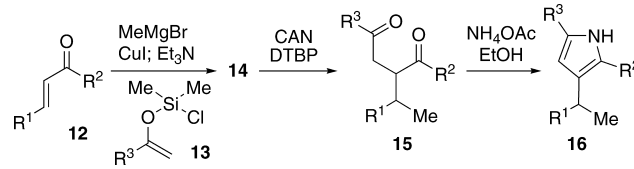
the more organic soluble base, 2,6-di-*tert*-butylpyridine (DTBP), reasoning that it might more effectively suppress undesired substrate breakdown by the acidic ammonium counterions of CAN. Under these conditions at −20 °C, we could obtain the diketone **11** in an isolated yield of 50% (Table 1, entry 6).

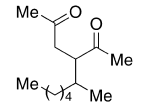
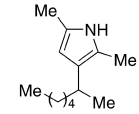
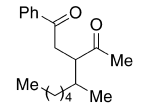
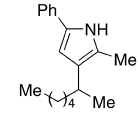
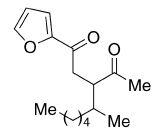
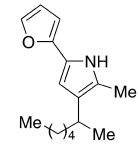
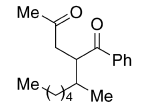
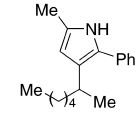
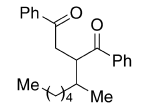
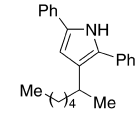
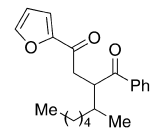
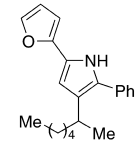
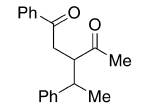
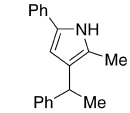
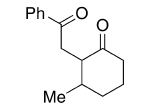
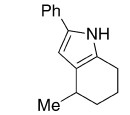
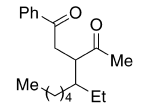
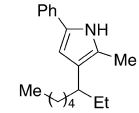
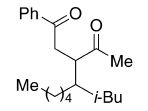
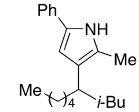
With these developed conditions in hand, we next investigated the scope of the reaction using a number of enones, chloro enol silanes, and Grignard reagents (Table 2). While for the initial development of the oxidative coupling (i.e., Table 1) we used purified silyl bis-enol ether **10**, purification of many silyl bis-enol ethers was a nontrivial task due to hydrolysis of the compounds on various chromatography supports. To circumvent this issue, we elected to conduct the oxidative coupling using the unpurified silyl bis-enol ethers formed from the initial addition and enolate silylation. This modification proved satisfactory, since the 1,4-addition/silylation typically proceeded cleanly and efficiently. Still working in the racemic series, 1,4-addition of the cuprate derived from methylmagnesium bromide to the enone **12** (R^1 = *n*-pentyl, R^2 = Me) proceeded smoothly to generate the intermediate enolate, which could be trapped effectively with the chlorosilane (i.e., **13**) derived from acetone, acetophenone, or 2-acetylfuran (Table 2, entries 1−3). The unpurified unsymmetrical silyl bis-enol ethers thus formed (i.e., **14**) were then subjected to conditions for oxidative coupling; enone **8** (R^1 = *n*-pentyl, R^2 = Me) afforded the 1,4-diketone in 47%, 54%, and 56% for entries 1−3, respectively. The phenyl ketone-containing enone (R^1 = *n*-pentyl, R^2 = Ph) gave the analogous adducts in similar yields (51−58%, entries 4−6), and styrlic enone (R^1 = Ph, R^2 = Me) also proved to be effective (56% yield, entry 7). The reaction sequence could be performed using cyclohexenone to provide the cross-coupled acetophenone adduct in 54% yield (Table 2, entry 8). We also investigated the conjugate addition of ethyl and isobutyl groups, as these would be directly relevant to our proposed prodigiosin syntheses. For each case, the 1,4-diketone was formed in good yield over the two-step addition/oxidation sequence (Table 2, entries 9 and 10).

For all substrates investigated, the diastereoselectivity of the oxidative bond formation was poor, but this was of no consequence for our immediate purpose, as we planned to convert the diones into the corresponding pyrroles. Standard Paal−Knorr pyrrole synthesis proceeded smoothly to provide the pyrroles in high yields (85−94%). Taken as a whole, the results shown in Table 2 demonstrate the utility of this merged conjugate addition/oxidative coupling sequence for generating highly substituted pyrroles from simple building blocks.

Total Synthesis. With a general method for merged conjugate addition/oxidative coupling established, we turned our focus to constructing the prodigiosin alkaloids. Our synthesis of metacycloprodigiosin (**1**) began with enone **6**, which could be prepared in two steps from commercially available oct-7-ene-1,2-diol (Scheme 2).[16] We elected to conduct the enantioselective addition of the requisite ethyl group using the system developed by Feringa and co-workers, which had been shown to afford a high degree of both regio- and enantioselectivity for similar substrates.[17] In the event, the copper-catalyzed addition

Table 2. Merged Sequence Applied to Pyrrole Synthesis



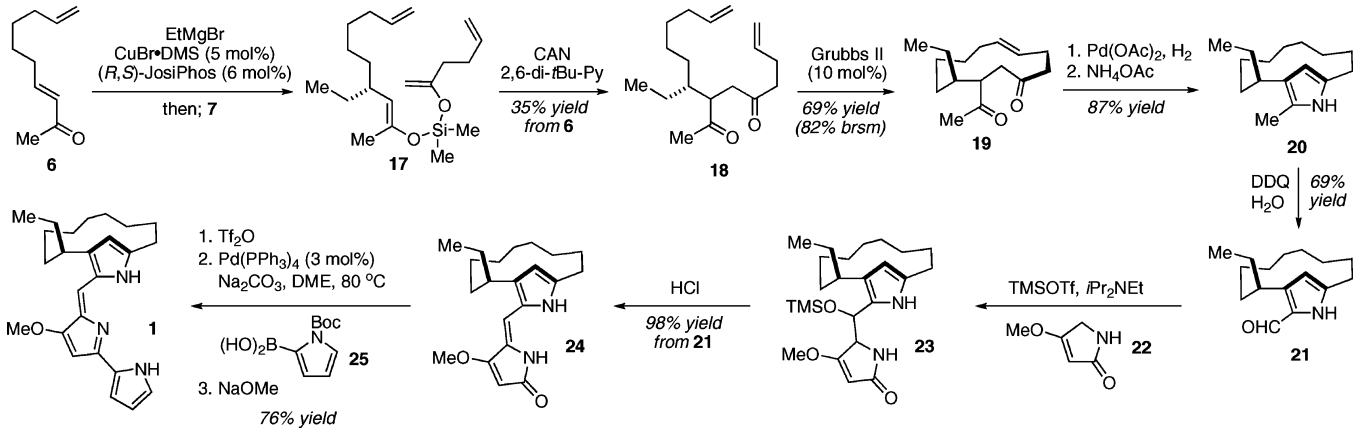
entry	R^1, R^2 R^3	1,4-diketone (**15**)	yield (%)[a] (d.r.)[b]	pyrrole (**16**)	yield (%)[c]
1	C_5H_{11}, Me Me		47 (2:1)		86
2	C_5H_{11}, Me Ph		54 (1.3:1)		92
3	C_5H_{11}, Me 2-furyl		56 (1.7:1)		89
4	C_5H_{11}, Ph Me		51 (1.8:1)		94
5	C_5H_{11}, Ph Ph		51 (2:1)		91
6	C_5H_{11}, Ph 2-furyl		58 (1.6:1)		89
7	Ph, Me Ph		56 (2:1)		87
8	-$(CH_2)_3$- Ph		54 (1.7:1)		85
9[d]	C_5H_{11}, Me Ph		57 (1:1)		92
10[e]	C_5H_{11}, Me Ph		58 (1:1)		87

[a] Isolated yield over two steps from enone **12**. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield from 1,4-diketone **15**. [d] EtMgBr used in 1,4-addition. [e] *i*-BuMgBr used in 1,4-addition.

(16) See Supporting Information for details.

(17) Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784–12785. The same catalyst system was used by Feringa and co-workers in a tandem conjugate addition/aldol reaction with acrylate derivatives, see: Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977–14985.

Scheme 2. Enantioselective Synthesis of Metacycloprodigiosin (**1**)



of ethylmagnesium bromide to enone **6** using 6 mol % (*R*,*S*)-JosiPhos proceeded smoothly, and the intermediate enolate could be trapped with chlorosilane **7** to give the silyl bis-enol ether **17** as a mixture of enol isomers. A small portion of this material was hydrolyzed to the corresponding ketone, which was determined to be a 93:7 mixture of enantiomers.[18] Typically, however, unpurified bis-enol **17** was subjected directly to the conditions for oxidative bond formation. Thus, using our developed conditions (CAN/2,6-di-*t*-Bu-pyridine, 0 °C) dione **18** could be formed in 35% yield over the two steps from enone **6**.[19] The generation of **18** as a mixture of diastereomers was inconsequential to our synthesis plan, since the stereocenter adjacent to the ketone would ultimately be destroyed upon pyrrole formation (i.e., **20**). Construction of the requisite 12-membered ring was achieved in 69% yield (82% based on recovered starting material) with minimal levels of dimer formation (<10%) by treatment of dione **18** with 10 mol % of Grubbs second-generation catalyst.[20] Hydrogenation with H_2/$Pd(OH)_2$ gave the fully saturated system, which was cleanly converted to the pyrrole **20** upon exposure to NH_4OAc in ethanol (87% yield, two steps).

Installation of the bispyrrole side arm of metacycloprodigiosin (**1**) began with oxidation of the methyl group within **20** to the corresponding aldehyde. A variety of conditions were examined to effect this transformation, including the CAN-mediated oxidation reported by Fürstner and co-workers for a similar substrate.[21] These conditions resulted in substantial decomposition of the substrate; ultimately, we found that exposure of **20** to dichlorodicyanoquinone in a solution of aqueous acetonitrile afforded the aldehyde (i.e., **21**) with the fewest side products (69% yield). At this juncture, our plan was to install the two pyrrole units by direct analogy to the procedure utilized by D'Alessio and co-workers in their synthesis of the less complex molecule, undecylprodigiosin.[22] We therefore anticipated a base-promoted aldol condensation between aldehyde **21** and lactam **22** to afford **24**, which would then undergo triflation and Suzuki coupling to provide the natural product. In practice, aldehyde **21** proved surprisingly resistant to addition of the lactam under a variety of basic conditions. During investigations into an alternative strategy, we found that aldehyde **21** underwent smooth condensation with hydroxylamine to form the corresponding oxime, providing evidence that the aldehyde function was not completely immune to nucleophilic addition. In the case of oxime formation, the reaction was most likely driven to completion by rapid loss of water from the initial tetrahedral intermediate, whereas for the addition of lactam **18** under basic conditions, it appeared that a retro vinylogous-aldol reaction was favored over dehydration. We reasoned that silylation of the intermediate aldolate to form ether **23** would solve this problem and allow for dehydration under acidic conditions. In practice, a trimethylsilyltriflate-mediated direct aldol reaction[23] gave ether **23** as a mixture of diastereomers, which upon exposure to HCl in tetrahydrofuran (THF) provided the requisite lactam **24** (98% from **21**). Addition of aqueous KOH to the mixture of ethers (i.e., **23**) resulted in clean regeneration of aldehyde **21**, providing support for our retro vinylogous-aldol hypothesis.

Completion of the synthesis entailed triflation, followed by Suzuki cross-coupling with pyrrole **25**, which afforded metacycloprodigiosin (**1**) in 76% yield, after removal of the Boc-group. Spectroscopic data (^1H and ^{13}C NMR, MS) were identical to those of the natural product.[24] The synthesis required 11 steps from enone **6** and proceeded in 13% overall yield. We applied this same strategy to complete the first total synthesis[25] of the recently isolated molecule, prodigiosin R1 (**2**, Scheme 3).[9] These

(18) Enantiopurity determined by GC with a chiral stationary phase. The absolute configuration was determined by conversion of the hydrolyzed ketone into known (*R*)-(−)-2-ethyloctan-1-ol and subsequent comparison of the optical rotation: Norsikian, S.; Baudry, M.; Normant, J. F. *Tetrahedron Lett.* **2000**, *41*, 6575–6578. The sense of induction is consistent with those reported by Feringa and co-workers in ref 17; see Supporting Information for further details.

(19) The lower yield for this substrate is most likely due to the presence of the pendant alkenes, which could potentially cyclize onto the radical-cation intermediates. Although we could not identify any such cyclized products, the oxidative coupling of the corresponding fully saturated analogue of **17** proceeded in a more reasonable 47% yield, in line with the results in Table 2.

(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(21) Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2777–2781.

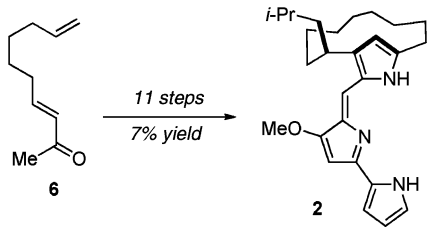
(22) D'Alessio, R.; Rossi, A. *Syn. Lett.* **1996**, 513–514. For related strategies applied to prodigiosin alkaloids, see also: Reeves, J. T. *Org. Lett.* **2007**, *9*, 1879–1881and ref 17.

(23) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Burreddu, P.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2008**, *73*, 5446–5451. For a related example of a direct aldol reaction mediated by TMSOTf, see: Downey, C. W.; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559–3562.

(24) Compared with the data reported by Gu and co-workers: Liu, R.; Cui, C.-B.; Duan, L.; Gu, Q.-Q.; Zhu, W.-M. *Arch. Pharm. Res.* **2005**, *28*, 1341–1344.

(25) See Supporting Information for full details of the prodigiosin R1 synthesis.

Scheme 3. Enantioselective Synthesis of Prodigiosin R1 (**2**)



two syntheses represent the first time that any members of the prodigiosin alkaloids have been prepared in enantioenriched form.

Conclusions

By developing a merged conjugate addition/oxidative coupling sequence, we have been able to access diverse pyrrole structures through the combination of three readily accessible components (i.e., Grignard reagent, enone, and enol silane). Crucial to the success of this procedure was the generation of a silyl bis-enol ether intermediate, which ensured selective cross-coupling during the oxidative bond-forming step, rather than potential dimerization pathways. When the conjugate addition was conducted with a chiral catalyst, efficient asymmetric induction could be achieved, and this allowed for the first enantioselective total syntheses of metacycoprodigiosin and prodigiosin R1. This general strategy for preparing enantioenriched prodigiosins has important implications for future biological studies of these intriguing molecules. Additionally, the merged process we have developed generates pyrroles possessing a stereocenter attached to C3 and is complementary to the enantioselective Friedel−Crafts alkylation of pyrroles, which produces a stereocenter at C2.[26]

Experimental Section[27]

General Procedure for the Merged Conjugate Addition/Oxidative Coupling Sequence. To a vigorously stirred suspension of CuI (232 mg, 1.22 mmol) in THF (7 mL) at 0 °C was added dropwise the Grignard reagent (1.20 mmol, solution in diethyl ether). The resulting suspension was stirred for 20 min at that temperature, and then the enone (1.0 mmol) was added dropwise as a solution in THF (2 mL, then 1 mL rinse). The mixture was allowed to stir for 30 min prior to dropwise addition of the (chloro)silyl enol ether [generated *in situ* by dropwise addition of acetyl chloride (85 μL, 1.20 mmol) to a solution of the appropriate (diethylamino)silyl enol ether (1.22 mmol) in THF (5 mL) at 0 °C, followed by stirring for 20 min], followed by dropwise addition of triethylamine (420 μL, 3 mmol). The reaction mixture was allowed to stir at 0 °C until deemed complete by thin-layer chromatography (TLC) (typically between 1 and 5 h) and then quenched by slow addition of saturated NH_4Cl (1 mL). The mixture was diluted with pentane (15 mL), poured into 20% NH_4OH (20 mL), and shaken vigorously, and the organic layer removed. The aqueous phase was further extracted with pentane (2 × 15 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was used directly in the subsequent oxidation. To a solution of CAN (1.21 g, 2.2 mmol) in MeCN (23 mL) at −25 °C was added dropwise 2,6-di-*tert*-butylpyridine (972 μL, 4.4 mmol). After several minutes, to the resulting solution was added the silyl bis-enol ether **10** as a solution in MeCN (5 mL, then 2 mL rinse, cooled to −25 °C prior to addition). The reaction was stirred at −20 °C (unless otherwise noted) until deemed complete by TLC analysis (typically between 12 and 24 h). The mixture was then poured into saturated $NaHCO_3$ (30 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were then washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel provided the desired diketones as inseparable mixtures of diastereomers.

General Procedure for Pyrrole Synthesis. To a solution of 1,4-diketone (0.15 mmol) in EtOH (1.5 mL) was added ammonium acetate (116 mg, 1.15 mmol); the mixture was heated to reflux until the reaction was deemed complete by TLC analysis (typically between 30 min and 24 h). The resulting solution was then cooled to ambient temperature, diluted with $CHCl_3$ (5 mL), and poured into 1:1 saturated NH_4Cl:water (10 mL total), and the organic layer was extracted. The aqueous phase was washed with $CHCl_3$ (5 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (plug) on silica gel provided the desired pyrroles.

Metacycloprodigiosin (1): IR (film) 3431, 2936, 2848, 1595, 1235 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 12.79 (bs, 1H), 12.65 (bs, 1H), 12.59 (bs, 1H), 7.23 (t, 1H, J = 0.7 Hz), 7.06 (s, 1H), 6.93−6.92 (m, 1H), 6.36−6.35 (m, 1H), 6.27 (d, 1H, J = 1.6 Hz), 6.10 (s, 1H), 4.03 (s, 3H), 3.23−3.20 (m, 1H), 2.78−2.75 (m, 1H), 2.57−2.55 (m, 1H), 1.82−1.58 (m, 5H), 1.55−1.32 (m, 3H), 1.25−1.23 (m, 2H), 1.08−1.05 (m, 2H), 0.89 (t, 3H, J = 6.2 Hz), 0.88 (obs m, 2H), 0.26−0.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.7, 154.3, 150.4, 147.4, 126.8, 126.0, 122.3, 120.6, 116.8, 113.3, 112.4, 111.6, 92.7, 58.7, 39.4, 34.4, 29.9, 29.0, 27.3, 26.8, 26.6, 25.6, 24.5, 22.8, 12.6; HMRS (ESI), exact mass calcd for $C_{25}H_{33}N_3O$ [M + H^+] 391.2624, found 391.2621.

Prodigiosin R1 (2): IR (film) 3135, 2920, 2856, 1610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 12.76 (bs, 1H), 12.62 (bs, 1H), 12.54 (bs, 1H), 7.21 (s, 1H), 7.06 (s, 1H), 6.91−6.90 (m, 1H), 6.34−6.33 (m, 1H), 6.24 (s, 1H), 6.08 (d, 1H, J = 1.8 Hz), 4.00 (s, 3H), 3.20−3.18 (m, 1H), 2.75−2.73 (m, 2H), 1.84−1.63 (m, 4H), 1.58 (td, 1H, J = 3.7, 1.7 Hz), 1.56−1.35 (m, 6H), 1.34−1.13 (m, 2H), 1.10−0.98 (m, 2H), 0.88 (d, 3H, J = 6.4 Hz), 0.84 (d, 3H, J = 6. Hz), 0.19−0.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.7, 154.3, 150.6, 147.5, 126.9, 125.7, 122.3, 120.6, 116.8, 113.2, 112.4, 111.6, 92.7, 58.8, 46.6, 35.5, 35.2, 29.0, 27.5, 26.8, 26.6, 26.0, 25.5, 24.5, 23.7, 22.4, 22.1; HMRS (ESI), exact mass calcd for $C_{27}H_{38}N_3O$ [M + H^+] 420.3009, found 420.3030.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA906122G

(26) For examples, see: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371. (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155. (c) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249–2252. (d) Trost, B. M.; Muller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438–2439.

(27) See Supporting Information for full experimental procedures.