ORGANIC LETTERS

2005
Vol. 7, No. 6
1063−1066

Synthesis of the Eastern Portion of Ajudazol A Based on Stille Coupling and Double Acetylene Carbocupration

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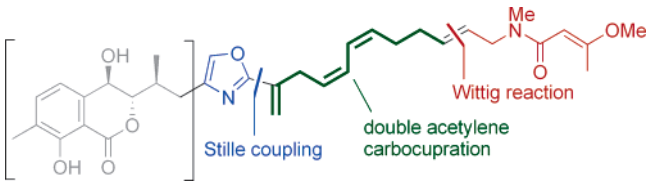
Received December 30, 2004

ABSTRACT



A strategy for the synthesis of ajudazol A, an unusual, pharmacologically active metabolite from myxobacteria, based on the Stille cross-coupling of a 2-stannyl-oxazole with a vinyl iodide unit is described; the vinyl halide unit containing a (*Z*,*Z*)-diene was prepared in one pot by the double acetylene carbocupration of a functionalized alkyl cuprate followed by trapping with 2,3-dibromopropene.

There is increasing interest in novel, bioactive natural products produced by myxobacteria. Myxobacteria are "social bacteria" often found in animal dung and organic-rich soils, some of which secrete antibiotics to kill other bacteria that are then digested.[1] The myxobacteria *Chondromyces crocatus* has proved to be a rich source of bioactive natural products that include the cytostatic chondramides[2] and the crocacins,[3] which inhibit the growth of fungi and yeasts by interfering with electron flow within cytochromes in the respiratory chain. More recent studies by Jansen et al. have resulted in the isolation of two additional, novel natural products from *C. crocatus*, which were named ajudazol A and ajudazol B.[4] Extensive spectroscopic studies (HRMS, IR, and UV but mainly two-dimensional NMR) resulted in the assignment of the novel dihydroxylated methylisochromanone structures **1a** and **1b** as shown in Figure 1.

In addition to the unusual isochromanone moiety, the terminal *N*-methyl amide of 3-methoxybutenoic acid is apparently unprecedented, as is the oxazole-linked polyene fragment. The internal (*Z*,*Z*)-diene unit is also an unusual feature in myxobacterial natural products, although examples are known from other natural sources (see below). In later studies, the ajudazols were shown to be antimicrobial agents

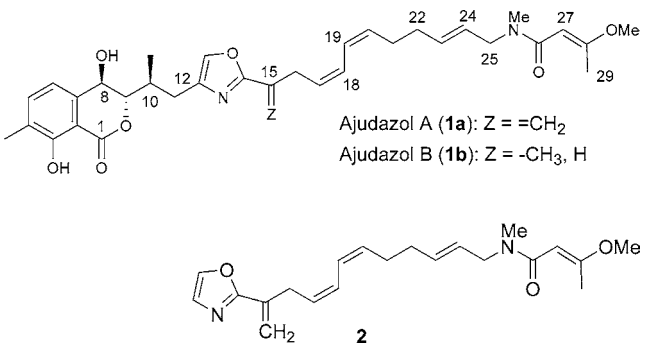


Figure 1. Ajudazols A (**1a**) and B (**1b**) [only one enantiomer is shown, although their absolute configuration is not known (nor is the configuration at C-15 in ajudazol B)] and synthetic analogue **2**.

(1) (a) Reichenbach, H.; Höfle, G. In *Drug Discovery from Nature*; Grabley, S., Thiericke R., Eds.; Springer-Verlag: Berlin, 1999; pp 149−187. (b) Höfle, G.; Reichenbach, H. The Biosynthetic Potential of Myxobacteria. In *Sekundärmetabolismus bei Mikroorganismen*; Kuhn, W., Fiedler, H.-P., Eds.; Attempto Verlag: Tübingen, 1995; pp 61−78.

(2) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1996**, 285−290.

(3) Sasse, F.; Kunze, B.; Gronewold, T. M. A.; Reichenbach, H. *J. Natl. Cancer Inst.* **1998**, *90*, 1559−2563 and references therein.

(4) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2002**, 917−921.

10.1021/ol047313+ CCC: $30.25
Published on Web 02/23/2005

that also inhibit mitochondrial electron transport.[5] Thus, the ajudazols are interesting synthetic targets, and substructure bioassay should shed light on their mode of action. In this Letter, we outline our synthetic approach to ajudazol A and illustrate the viability of this approach by describing the successful preparation of analogue **2**, which possesses the oxazole ring and the complete eastern side chain.

The retrosynthetic analysis, shown in Figure 2, is based on the key Stille disconnection, which generates the substituted 2-stannyl-oxazole **3** and an eastern side chain unit **4**, terminated by a vinylic halide function. This convergent route involving the introduction of the complete eastern side chain at a late stage of the synthesis was devised to minimize the chances of intramolecular reactions between the oxazole or chromanone portions of the molecule and reactive intermediates needed during the construction of the polyene side chain.

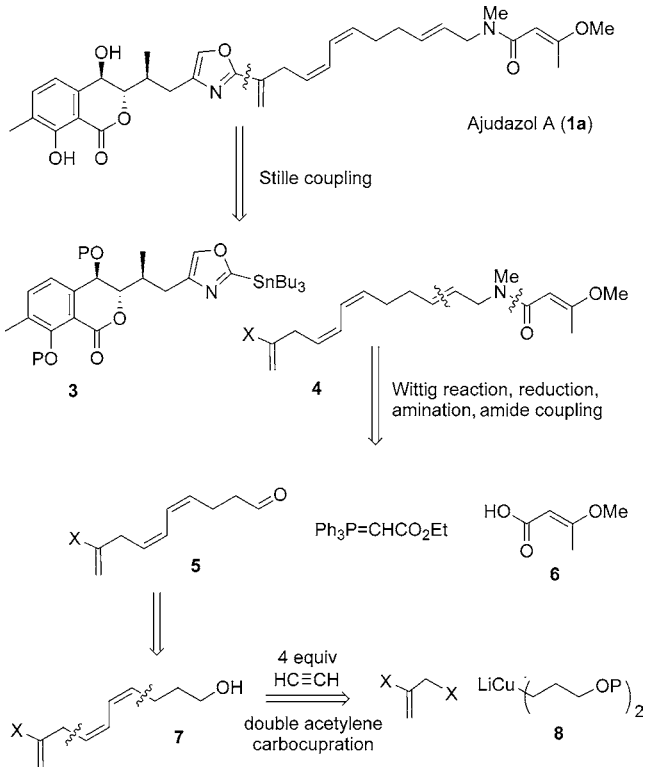
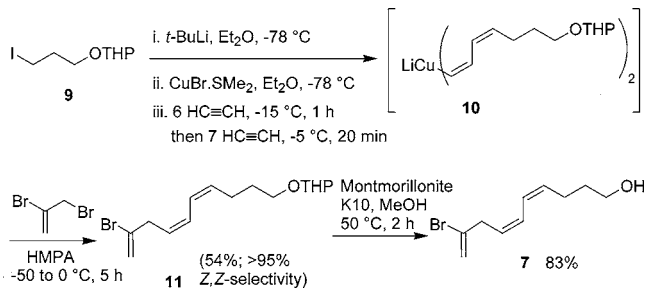


Figure 2. Retrosynthesis of ajudazol A (**1a**); in practice, a measured excess of acetylene gas is required in the final step depicted.

We decided to test the viability of this Stille coupling approach using 2-tributylstannyloxazole (as a model for **3**) and vinyl halide **4**. Retrosynthetic analysis of side chain **4** suggested an amide coupling with 3-methoxybutenoic acid **6** in the final step and an (*E*)-stereoselective Wittig reaction on aldehyde **5** to produce a suitable precursor. The (*Z*,*Z*)-dienyl aldehyde **5** would be available from alcohol **7**, which therefore became the first target for this study. (*Z*,*Z*)-Diene units are increasingly common in natural products,[6] and some time ago we developed a double acetylene carbocupration procedure for their stereocontrolled synthesis.[7] This methodology was utilized to prepare the Navel orangeworm pheromone[7] and has subsequently been employed by other groups to prepare insect pheromones,[8] the myxobacteria-derived apicularens,[9] and salicylihalamide A, isolated from a marine sponge.[9,10] Double acetylene carbocupration is a variant of the Normant reaction[11] in which organocuprates react with four molecules of acetylene to give the corresponding four-carbon homologated (*Z*,*Z*)-dienyl cuprates, which can be trapped to produce (*Z*,*Z*)-dienes via a one-pot process with excellent stereocontrol.[7]

To date, the double acetylene carbocupration procedure has always been carried out with unfunctionalized di(alkyl)-cuprates. The synthesis of target molecule **7** (Scheme 1) is

Scheme 1



therefore noteworthy in that it employs the tetrahydropyranyloxypropylcuprate **8** derived from the readily available[12] THP-protected 3-iodopropanol **9**. Treatment of **9** with 2 equiv of *t*-BuLi at −78 °C followed by addition of CuBr·SMe_2 produced the functionalized dialkylcuprate **8** as a clear solution. Addition of 6 equiv of acetylene (gas buret) at −15 °C over 1 h generated a dark-green solution of the presumed vinyl cuprate, and an additional 7 equiv of acetylene was then added at −5 °C over 20 min to produce the desired (*Z*,*Z*)-dienyl cuprate **10**. The solution was immediately cooled to −40 °C, and 2,3-dibromopropene in HMPA was added, giving, after workup and chromatography (SiO_2−$AgNO_3$;

(5) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *J. Antibiot.* **2004**, *57*, 151−155.

(6) (a) Sirirath, S.; Tanaka, J.; Ohtani, I. I.; Ichiba, T.; Rachmat, R.; Ueda, K.; Usui, T.; Osada, H.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1820−1823. (b) Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048−4049. (c) Wipf, P.; Graham, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 15346−15347 and references therein.

(7) (a) Furber, M.; Taylor, R. J. K.; Burford, S. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1809−1815. (b) Taylor, R. J. K.; Casy, G. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 2.

(8) Millar, J. G. *Tetrahedron Lett.* **1997**, *38*, 7971−7972.

(9) (a) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407−408. (b) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817−1820.

(10) Smith, A. B.; Zheng. J. *Tetrahedron* **2002**, *58*, 6455−6471.

(11) Normant, J.-F.; Alexakis, A. *Synthesis* **1981**, 841−870. (b) Normant, J.-F. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 11.

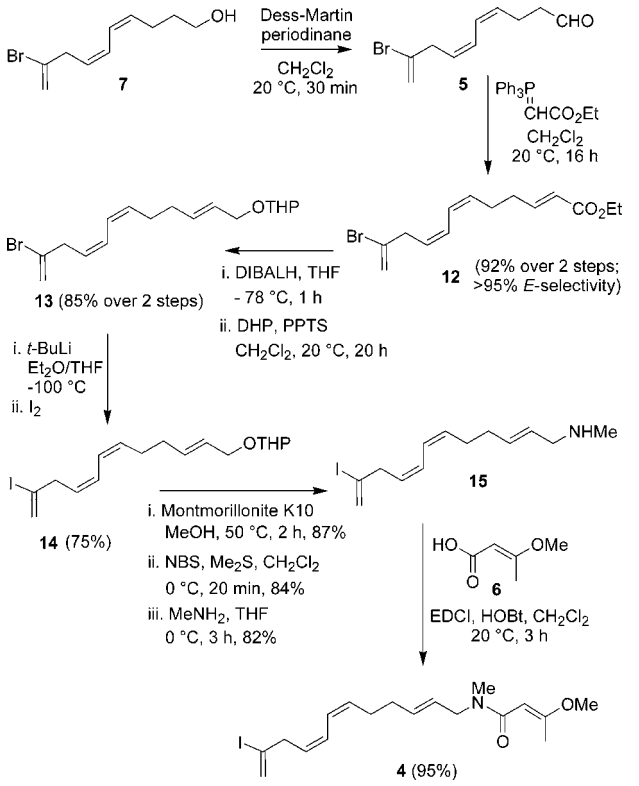
(12) Cox, G. G.; Moody, C. J.; Austin, D. J.; Padwa, A. *Tetrahedron* **1993**, *49*, 5109−5126.

to remove the (*Z*)-alkene resulting from simple carbocupration, 16%), the desired diene **11** in 54% yield on a 4 mmol scale. The (*Z*,*Z*)-configuration of the diene portion in **11** was confirmed by NMR spectroscopy of the internal diene protons (J = ca. 11 Hz). It should be noted that the corresponding sequence was also studied using other protecting groups for the 3-iodopropanol (TBDMS, TBDPS, TIPS, and MOM), as well as with 1,1-diethoxy-3-iodopropane, but without success. The THP-derived organocopper reagent was also less reactive in the carbocupration process than the corresponding unfunctionalized dialkylcuprates, but the acetylene insertions could be achieved by adding more acetylene gas at higher temperatures over a longer period according to the procedure mentioned above and described in detail in Supporting Information. The best solvent mixture for this double carbocupration was diethyl ether/hexane (ca. 4:1). With more polar solvents, acetylene deprotonation (formation of copper acetylide, CuC≡CR) occurred; in less polar mixtures, the vinyl/dienyl cuprate completely decomposed at the temperature of the second insertion step (−5 °C).[11,13] Stabilizing additives such as Me_2S or $P(OEt)_3$ prevented acetylene insertion. The resulting THP-protected diene **10** was deprotected to give the free alcohol **7** in 83% yield by stirring with Montmorillonite K10 in methanol.[14]

The alcohol **7** was oxidized using the Dess−Martin periodinane to give the corresponding aldehyde **5**, which was used immediately in a Wittig reaction with ethyl (triphenylphosphoranylidene)acetate to give the desired (*E*)-configured (J = 15.6 Hz) α,β-unsaturated ester **12** in 92% yield over the two steps (Scheme 2). The ester **12** was reduced with diisobutylaluminum hydride to the corresponding alcohol (85%), which was protected as the THP derivative **13** in quantitative yield. Subsequent studies revealed that the vinyl bromide (**4**, X= Br) was insufficiently reactive as a Stille coupling partner. We therefore carried out a halogen exchange by treating vinyl bromide **13** with *t*-BuLi and quenching the resulting organolithium reagent with iodine to produce vinyl iodide **14**. Compound **14** was then deprotected and the resulting alcohol converted into the corresponding bromide by treatment with dimethyl sulfide/NBS.[15] The use of PPh_3/CBr_4 occasionally gave higher yields but was unreliable. The bromide was then transformed into amine **15** by treatment with excess methylamine; all three reactions proceeded in yields of >80%. Amine **15** was then coupled with 3-methoxybutenoic acid to give the requisite Stille coupling partner **4** (X = I) in 95% yield.

3-Methoxybutenoic acid (**6**) was prepared from methyl acetoacetate in 50% overall yield by treatment with trimethyl orthoformate according to a literature procedure[16] followed by hydrolysis of the intermediate ester with lithium hydroxide.[17] Other syntheses of **6** are available,[18] but the procedure

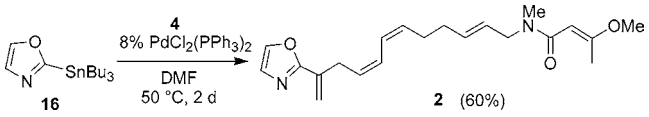
Scheme 2



described gives the acid exclusively as the (*E*)-isomer (confirmed by NOESY) in high purity.

The Stille coupling of side chain **4** (X = I) with 2-(tributylstannyl)oxazole (**16**)[19] was investigated next (Scheme 3). It should be noted that no success was achieved in the

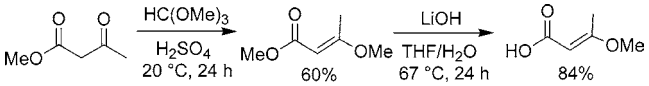
Scheme 3



coupling of **16** with the vinyl bromide **4** (X = Br): temperatures of ca. 100 °C were required before any reaction was observed, but at these temperatures the diene system proved to be unstable. A range of palladium catalysts, including $Pd(PPh_3)_4$ and $PdCl_2(NCMe)_2$, were employed for the Stille coupling of **4** (X = I) with 2-(tributylstannyl)-oxazole (**16**), but the best yields were obtained using

(13) Normant, J.-F.; Cahiez, G.; Bourgain, M.; Chuit, C.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 1656−1660.
(14) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K.; *Tetrahedron Lett.* **1997**, *38*, 1881−1884.
(15) Grdina, M. B.; Orfanopoulos, M.; Stephenson, L. M. *J. Org. Chem.* **1979**, *44*, 2936−2937.
(16) Smissman, E. E.; Voldeng, A. N. *J. Org. Chem.* **1964**, *29*, 3161−3165.

(17) Preparation of (*E*)-3-methoxybutenoic acid (**6**):



(18) Kresge, A. J.; Ubysz, D. *J. Phys. Org. Chem.* **1994**, *32*, 316−322. Zanatta, N.; de Cortelli, M. F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509−514.
(19) Dondoni, A.; Fogagnolo, M.; Medici, A.; Negrini, E. *Synthesis* **1987**, 185−187.

$PdCl_2(PPh_3)_2$ in DMF at 50 °C, which gave the required adduct **2** in 60% yield. Compound **2** was fully characterized (including HRMS). Unlike ajudazol A,[4] compound **6** appears to be stable during silica gel chromatography and at higher temperatures (80 °C). The thermal and acid sensitivity of **1a** therefore appears to be associated with the hydroxyisochromanone portion.

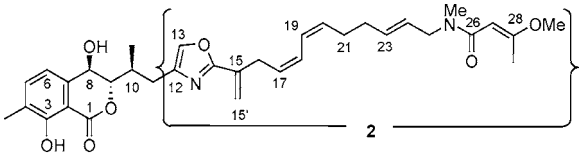
Compound **2** is a close analogue of ajudazol A (**1a**) but lacks the isochromanone side chain at the oxazole C-12 site. The NMR data for **2** were therefore compared with those reported[4] for ajudazol A (**1a**) as shown in Table 1.

As can be seen, the ^1H and ^{13}C NMR data of both compounds are in good accord, providing strong support for the proposed structure, particularly for the unusual structural features of ajudazol A such as the (*Z*,*Z*)-diene functionality, the *exo*-methylene group, and the *N*-methyl methoxybutenoic acid amide. In addition, both compounds ajudazol A and analogue **2** show a distinct UV absorption at 320 nm in methanol.

In summary, double acetylene carbocupration using a functionalized alkylcuprate and 2,3-dibromopropene as the trapping reagent was employed as the cornerstone of a synthesis of the polyene side chain of ajudazol A, an antimicrobial agent isolated from the myxobacteria *Chondromyces crocatus*. This new methodology (using functionalized cuprates) could be useful for the preparation of other (*Z*,*Z*)-diene-containing natural products such as the bitungolides A−F,[6a] leustroducsin B,[6b] or disorazole C.[6c] In addition, a Stille coupling procedure has been developed to link the polyene side chain vinyl iodide and 2-(tributylstannyl)oxazole to produce the novel ajudazol A analogue **2**, which lacks only the isochromanone side chain at the oxazole C-12 site. We are currently utilizing the methodology described herein to complete a synthesis of ajudazol A itself.

Acknowledgment. The Deutsche Forschungs-gemeinschaft (German Research Foundation) and the Alexander von Humboldt Foundation are thanked for postdoctoral support (O.K.). We also thank Gail Young (University of York) for many helpful discussions.

Table 1. Comparison of the NMR Data of Ajudazol A (**1a**) and Analogue **2**



Ajudazol A (**1a**)

	synthetic **2**		ajudazol A (**1a**)[4]	
C[a]	^1H[b]	^{13}C[b]	^1H[b]	^{13}C[b]
14		161.0		161.0
15		134.0		134.4
15′	5.44/5.95 (2 × bs)	117.0	5.85/5.35 (2 × bs)	117.4
16	3.39 (d, 7.6 Hz)	29.7	3.27 (d, J = 7.8 Hz)	30.0
17	5.39−5.61 (m)	127.6	5.52 (m)	127.6
18[c,d]	6.33 (dd, 10.7 Hz)	124.8	6.29 (dd, ∼11 Hz)	125.2
19[c,d]	6.40 (dd, 10.7 Hz)	123.2	6.37 (dd, ∼11 Hz)	123.6
20	5.39−5.61 (m)	131.5	5.45 (m)	132.0
21[d]	2.15 (dt, 7.0 Hz)	26.4	2.19 (m)	26.8
22[d]	2.28 (dt, 7.3 Hz)	31.0	2.08 (m)	31.4
23	5.39−5.61 (m)	131.4	5.54 (ddt)	132.0
24	5.39−5.61 (m)	125.5	5.39 (m)	125.7
25[e]	3.90 (d, 6.0 Hz)	49.6	3.84 (d, 5.7 Hz)	50.1
NMe[e]	2.87 (s)	33.2	2.82 (s)	35.0
26[e]		168.1		168.0
27[e]	5.17 (s)	91.4	5.24 (s)	91.8
28		166.4		167.0
29	2.11 (s)	17.7	2.04 (s)	18.1
OMe[e]	3.60 (s)	54.3	3.53 (s)	54.8

[a] Data for carbons 1−13 are given in ref 4. [b] In DMSO-d_6 at 80 °C, if not stated otherwise. [c] In $CDCl_3$ at 50/55 °C. [d] $J_1 = J_2$. [e] Doubling of the ^1H and ^{13}C NMR signals at room temperature is observed for both compounds.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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