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Full Stereochemical Determination of Ajudazols A and B by Bioinformatics Gene Cluster Analysis and Total Synthesis of Ajudazol B by an Asymmetric Ortholithiation Strategy

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Supporting Information

ABSTRACT: The stereochemical determination of the potent respiratory chain inhibitors ajudazols A and B and the total synthesis of ajudazol B are reported. Configurational assignment was exclusively based on biosynthetic gene cluster analysis of both ketoreductase domains for hydroxyl-bearing stereocenters and one of the first predictive enoylreductase alignments for methyl-bearing stereocenters. The expedient total synthesis resulting in unambiguous proof of the predicted stereochemistry involves a short stereoselective approach to the challenging isochromanone stereotriad by an innovative asymmetric ortholithiation strategy, a modular oxazole formation, and a late-stage *Z*,*Z*-selective Suzuki coupling.

The varied architectures of natural products continue to present formidable inspirations for new methods of structure elucidation and directed synthesis. In recent years, innovative combinations of genetic and chemical tools have become more and more important in enabling novel analytical and synthetic techniques.[1] In particular, secondary metabolites from myxobacteria have become increasingly well understood objects of study[2] for such approaches.[3] Ajudazols A (**1**) and B (**2**) (Figure 1) are structurally unique polyketides from the

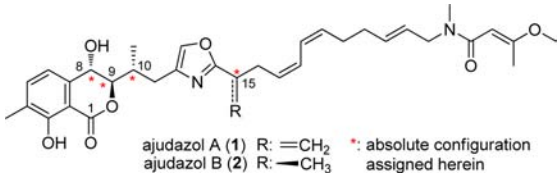

Figure 1. Ajudazols A (**1**) and B (**2**), potent mitochondrial respiratory chain inhibitors from the myxobacterium *C. crocatus*.

myxobacterium *Chondromyces crocatus*, stain Cm c5[4] that have proved to be highly effective inhibitors of the mitochondrial respiratory chain through selective binding to complex I (NADH-dehydrogenase).[5] The NADH oxidation level in beef heart submitochondrial particles was inhibited at an IC_{50} value of 13.0 ng/mL (22.0 nM) for **1** and 10.9 ng/mL (18.4 nM) for **2**. The mitochondrial respiratory chain represents the key mechanism for aerobic production of energy,[6] and dysfunctions contribute to various diseases[7] and were recently mentioned in the context of Parkinson's and Alzheimer's diseases.[8] This renders the detailed molecular understanding and development of effective and synthetically accessible inhibitors important research goals. The unique architecture of the ajudazols is characterized by an unusual isochromanone heterocycle bearing two vicinal anti-configured hydroxyl groups (C8 and C9) that is connected to an extended side chain incorporating an oxazole, a (*Z*,*Z*)-diene, and a terminal methoxybutenoic acid methylamide as characteristic features. While **1** bears an exomethylene group next to the oxazole, **2** has a methyl group at this position (C15). The ajudazols contain up to four stereocenters of unknown absolute configuration. Their potent biological properties, natural scarcity, and unique and intriguing molecular architecture render the ajudazols attractive targets, and several fragment syntheses have been reported.[9] However, these efforts have been severely hampered by apparent difficulties in establishing an efficient route to the isochromanone core and the lack of full stereochemical knowledge. In particular, the assignment of isolated methyl-bearing stereocenters[10] such as C15 in **2** poses a particular analytical challenge.

Herein we report the determination of the full stereochemistry of **1** and **2** and the first total synthesis of **2**, the more potent and less abundant ajudazol. Stereochemical assignment prior to the synthesis was based on a bioinformatics approach employing one of the first predictive enoylreductase (ER) alignments for the assignment of methyl groups. The total synthesis was based on an innovative approach to the isochromanone core that included an asymmetric ortholithiation strategy, modular oxazole formation, and a late-stage *Z*,*Z*-selective Suzuki coupling of elaborate substrates.

Stereochemically, the relative anti,anti configuration of C8−C10 has been proposed on the basis of conformational NMR studies.[4] In contrast, determination of the absolute configuration has been thwarted by the scarcity of similar natural products, the notable lability,[4] and the general difficulties associated with assigning isolated methyl-bearing stereocenters. Therefore, we turned our attention to a complementary approach relying on an analysis of the biosynthetic gene cluster.[11] In detail, the hydroxyl-

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bearing stereocenter at C9 is derived by a ketoreductase (KR)-mediated reduction of the corresponding ketone intermediate. The stereochemistry at the methyl-bearing C10 and C15 centers is dictated by ER-catalyzed reduction. The groups of McDaniel[12] and Caffrey[13] proposed a model for the observed selectivity of KRs that allows the configuration of secondary alcohols to be determined in a simple fashion by analysis of the amino acid sequence in the conserved core regions of the enzymes. In brief, the presence or absence of one amino acid, an aspartate (D) residue, corresponds to D-configured or L-configured alcohols, respectively. This method for configurational assignment of hydroxyl-bearing stereocenters has proved to be successful in a number of cases.[3a,b] Accordingly, analysis of the respective ajudazol gene cluster revealed a D residue in the KR core region responsible for the reduction to the alcohol at C9, suggesting that this stereocenter should be D (or *R*)-configured (Figure 2 top).

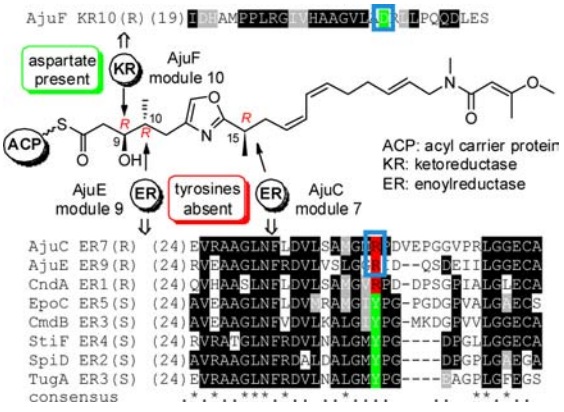

Figure 2. Bioinformatics-based configurational assignment of **2** by sequence alignment of (top) KR and (bottom) ER domains. The crucial amino acids for the prediction of stereochemistry are marked in blue boxes. The crucial tyrosine (Y) is absent in the ajudazol ERs, suggesting that the methyl-bearing stereocenters should be *R*-configured.

More recently, the group of Leadlay[14] analyzed ERs in an analogous fashion. Their study revealed that a tyrosine (Y) residue in the catalytic ER domain plays a critical role in the stereochemical outcome of this process. According to their model, the presence of this amino acid results in the formation of an *S*-configured methyl-bearing center, while its absence results in an *R* configuration. However, in contrast to existing studies on KRs, only a very limited number of partially contradictory[3c] examples have been analyzed, mainly from actinomycetes.[14] Therefore, we first evaluated the applicability of this method for stereochemical determination of myxobacterial metabolites by analyzing the biosynthetic gene cluster in direct comparison with the known stereochemical outcome (Figure 2 bottom). In all cases, perfect agreement was observed.[15] This enabled a confident assignment of the methyl-bearing C10 and C15 stereocenters. In detail, the absence of Y in the respective ER core regions suggested that these two centers should be *R*-configured. The full configurational assignment for **2** was therefore proposed to be 8*S*,9*R*,10*R*,15*R*, and on the basis of their common biogenesis, the stereochemistry of **1** was assigned accordingly (Figure 1).

Efforts were then directed to a validation of our assignment by the first total synthesis of **2**. As shown in Figure 3, our retrosynthetic analysis relied on two main subunits, a western fragment (**3**) and an eastern fragment (**5**). A modular late-stage introduction of the central methyl-bearing subunit (**4**) by

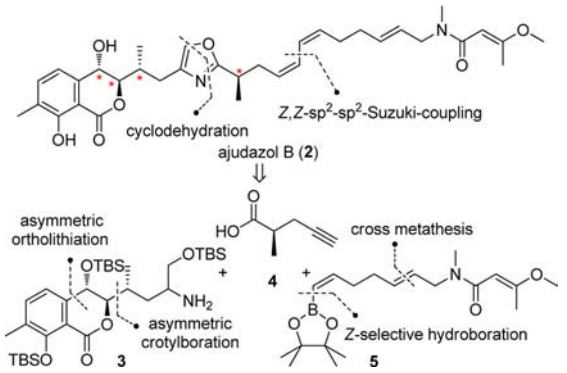

Figure 3. Retrosynthetic analysis of (+)-ajudazol B (**2**).

cyclodehydration with **3** for oxazole formation and *Z*,*Z*-selective Suzuki coupling[16] for connection with **5** was envisioned. A variable metathesis strategy would provide a basis for **5**. For construction of the labile isochromanone core, a conceptually novel approach relying on an innovative ortholithiation strategy was devised.[17] The Clayden group published pioneering studies[18] on an asymmetric variant[19] of this reaction. To generate the preferred atropisomer to mediate the electrophilic attack, they used a chiral amidosulfoxide as a temporary stereogenic center next to the directing metalation group. After cleavage of this stereocenter by ^{t}BuLi, the amide axis retains the chiral information in the sense of chiral memory. Capturing the resulting lithiated species with an aldehyde leads finally to self-regeneration of the stereocenter SRS-principle.[20] However, the applicability of this method has been thwarted by difficulties resulting from cleavage of the amide residue (required for asymmetric induction), the lability of the newly generated benzylic alcohol toward epimerization, and the limitation to five-membered rings,[19b] rendering this part of our route particularly challenging but also generally rewarding.

As the starting material for **3**, we chose commercially available 3-methylsalicylic acid (**6**), which already incorporates most of the aromatic substitution pattern. For protection of the phenolic hydroxyl, we used an allyl group, which proved to be stable enough during the subsequent ortholithiation and could be selectively removed later in the synthesis. After amide formation, the sterically hindered amide axis was fixed by ortholithiation and capture with the Andersen reagent[21] (**7**) to yield sulfoxide **8** (78% over four steps; Scheme 1, left). An orthogonal protecting group strategy was likewise required for OH-8 to secure exclusive formation of the six-membered lactone. The best results were obtained with orthogonal silyl protecting groups. In detail (Scheme 1 right), alcohol **10** was readily available from aldehyde **9** by a Brown crotylation (70%, 90% ee).[22] The absolute configuration was determined by Mosher ester analysis and independently at a later stage by X-ray structure analysis (see below). After triethylsilyl (TES) protection (99%), homologation of **10** involving hydroboration, oxidation, and Wittig reaction (80% over three steps) afforded ester **11**, which was transformed to the required slightly volatile aldehyde **12** by standard interconversions (86% over two steps). Gratifyingly, we were able to achieve the pivotal asymmetric coupling of lithiated **8** with **12** in high yield (80%) after slight modifications of the originally reported conditions, giving the desired anti,anti-configured product **13**[23] with high selectivity.[24] As anticipated,[19b] conversion of **13** into the desired isochromanone **14** proved challenging because of apparent difficulties in removing the stable tertiary amide without translactonizing the labile

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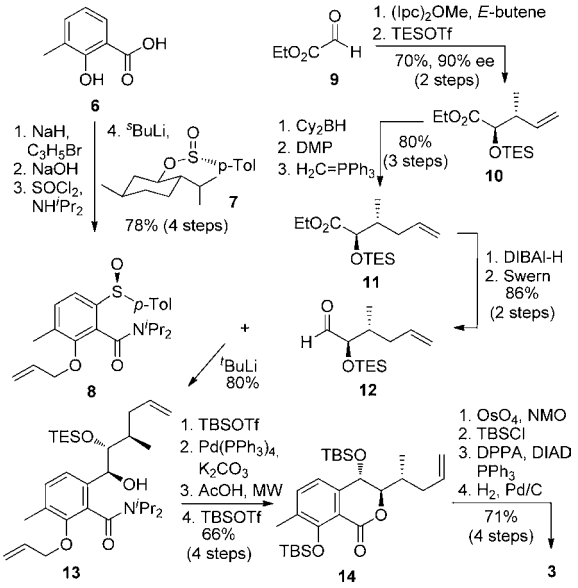
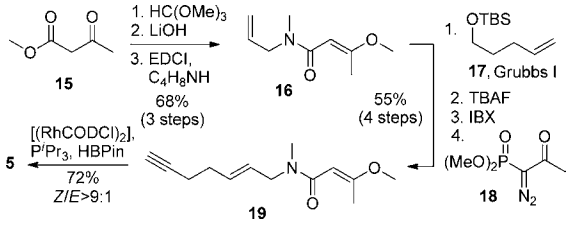
Scheme 1. Synthesis of Western Fragment 3



isochromanone and epimerizing the benzylic alcohol. Finally, the successful strategy was initiated by *tert*-butyldimethylsilyl (TBS) protection of the benzylic hydroxyl group (77%). Pd-mediated deprotection of the phenolic group then proved to be essential to enable the subsequent amide cleavage,[25] which after evaluation of diverse reagents and strategies was realized by refluxing a mixture of acetic acid in toluene. These conditions conserved the TBS protecting group and led to exclusive formation of the desired six-membered lactone with complete configurational retention. Notably, simultaneous cleavage of the TES group was achieved, adding to the effectiveness of this protocol. Microwave assistance (150 °C) improved the yield to 90% and reduced the reaction time from 7 days to 3 h. After unification of the protecting groups (TBSOTf, 2,6-lutidine, 95%), the absolute and relative configurations of **14** were confirmed by X-ray structure analysis of a structurally homologated product prepared in an analogous fashion.[26] Finally, **14** was transformed into the desired western fragment **3** by dihydroxylation of the terminal alkene, mono-TBS protection of the resulting primary alcohol, azide substitution[27] of the secondary alcohol, and hydrogenation (71% over four steps).

In contrast to previous approaches,[9a,b] our synthesis of **5** was based on an ambitious cross-metathesis[28] of allylic amine **16** with terminal alkene **17** (Scheme 2) to enable facile modifications of the side chain in the context of scheduled SAR studies. The synthesis of **16** was accomplished by conversion of methyl acetonate (**15**) into the corresponding enoic acid[9a] and amide coupling with *N*-allylmethylamine (68% yield over three steps). After optimization, the challenging coupling[29] with **17** was

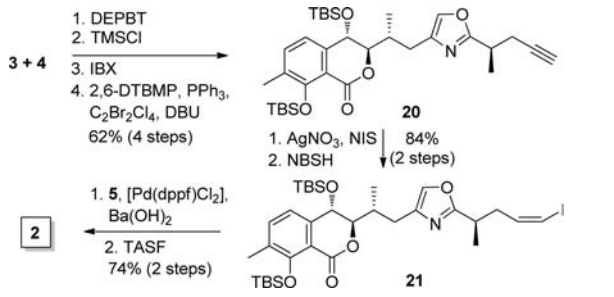
Scheme 2. Synthesis of Eastern Fragment 5



realized in reasonable yields based on concomitant recovery of starting material. After removal of the terminal TBS group, the free alcohol was oxidized, and the resulting aldehyde was homologated by an Ohira–Bestmann reaction[30] with **18** to give alkyne **19** in 55% yield over four steps. Finally, a Rh-catalyzed trans-hydroboration following the protocol of Miyaura[31] gave the desired eastern fragment **5** in reasonable yield and selectivity.

As shown in Scheme 3, completion of the total synthesis was initiated by amide coupling of amino alcohol **3** and acid **4**[32] with

Scheme 3. Completion of the Total Synthesis



DEPBT[33] followed by selective removal of the primary TBS group using catalytic amounts of TMSCl in water.[34] Oxazole formation by 2,4-cyclodehydration with IBX followed by treatment with DTBMP, PPh_3, $C_2Br_2Cl_4$, and DBU relied on a modified Wipf protocol[35] (78% over three steps). Stereoselective attachment of the side chain was then effected by iodination (NIS, $AgNO_3$) of alkyne **20**, transformation into the corresponding (*Z*)-vinyl iodide **21** by syn reduction with NBSH[36] (84% over two steps), and subsequent stereoselective Suzuki coupling[16] with **5** under mild conditions ($[Pd(dppf)Cl_2]$, $Ba(OH)_2$).[37] Concomitantly, cleavage of the phenolic TBS group was realized. Importantly, no signs of isomerization were observed. Finally, careful deprotection with buffered TASF[38] provided synthetic (+)-ajudazol B (**2**) in 74% yield over two steps. The ^1H and ^{13}C NMR data and specific rotation of our synthetic material were in agreement with those published for an authentic sample of ajudazol B (synthetic $[\alpha]_D^{21} = +7.9°$, $c = 0.9$, MeOH; natural $[\alpha]_D^{21} = +6.1°$, $c = 1.34$, MeOH), thus confirming the relative and absolute configuration of **2** and validating our bioinformatics-based assignment.

In conclusion, we have assigned the full stereochemistry of the ajudazols purely by an innovative bioinformatics approach. This involved gene cluster analyses of a ketoreductase domain for assignment of a hydroxyl-bearing center and one of the first applications of predictive enoylreductase-based determination of methyl-bearing stereocenters. This assignment was unequivocally validated by a total synthesis of ajudazol B (**2**), which represents the first total synthesis of the ajudazols in general and the first total synthesis based exclusively on stereochemical bioinformatics techniques. Our study documents the high reliability of modern genetic tools for structure elucidation, in particular for the determination of isolated methyl groups that are very difficult to assign by other means. Furthermore, our synthetic approach involves one of the first applications of an asymmetric ortholithiation strategy in complex target synthesis. Along these lines, we have reported effective substrate design and protocol developments that circumvent various problems previously associated with this method, including epimerizations, translactonizations, and eliminations of the product alcohols.

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These results will generally advance the use of asymmetric ortholithiations in functional target syntheses.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) It was unclear whether a second product that could not be separated from the sulfoxide byproducts was a diastereomer or an atropisomer. Thus, we could not determine the exact diastereomeric ratio. The given yield is for pure isolated diastereomer **13**, as diastereomers (potentially resulting from epimerization) can be differentiated by their NMR spectra (see section 2.11 in the SI).

(24) Without the chiral sulfoxide, product ratios of 2:1 were observed, presumably as a result of moderate Felkin–Anh control. In agreement with previous mechanistic studies,[18] the selectivites may be rationalized by the fixed amide axis (preoriented by the chiral sulfoxide), which controls the attack of the aldehyde from the preferred half-space by shielding the other half-space.

(25) Various previously published procedures for cleavage of tertiary amides resulted in no conversion or five-membered-ring formation.

(26) The stereochemistry of **14** was further confirmed by two additional X-ray structure analyses of deprotected derivatives of **13** (for full details, see the SI).

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