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Total Synthesis of the Antibiotic Elansolid B1

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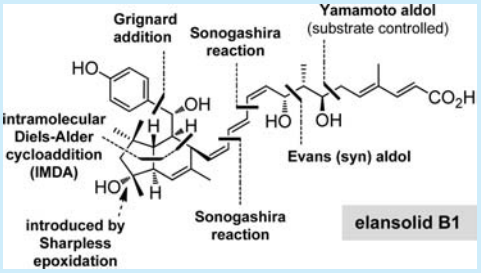
Supporting Information

ABSTRACT: The antibiotic elansolid B1 was prepared by a convergent strategy that relied on a highly diastereoselective, biomimetic intramolecular Diels–Alder cycloaddition (IMDA) that furnished the tetrahydroindane unit. Other key features are a double Sonogashira cross-coupling and a substrate-controlled Yamamoto aldol reaction.



Natural products continue to be an important source of inspiration for the development of medicines that have the potential to benefit human health and quality of life. There is a pressing need for the development of new antibiotics that operate through a novel mechanism and can combat resistance; indeed, most antibiotics are natural products or derivatives thereof. The elansolids comprise the first example of polyketides isolated from the gliding bacterium *Chitinophaga sancti* (formerly *Flexibacter*). They show antibacterial activity against several strains including methicillin-resistant *Staphylococcus aureus* MRS3 (MIC 0.3 μg mL^{-1}) and *Micrococcus luteus* (MIC 4.2 μg mL^{-1}).[1,2] Their core structure is based on a bicyclo[4.3.0]nonane unit. In the case of elansolids A1/A2 (**1**) this unit is part of a 19-membered macrolactone ring. The related seco acids elansolid B1 (**2a**) and elansolid B2 (**2b**) differ in the moiety present at C25. By employing careful isolation techniques the unique *p*-quinone methide elansolid A3 (**3**) could be obtained from the same culture broth (Figure 1).[2−4] This compound is key for understanding the occurrence of the other elansolids.

The uniqueness of **3** is evident when comparing it with the known triterpenoid celastrol,[5] the diterpenoid taxodone,[6] and the polyketide kendomycin[7] in which the *p*-quinone methide moiety is either stabilized by an extended conjugated system or by electron-donating groups, features that are absent in **3**.

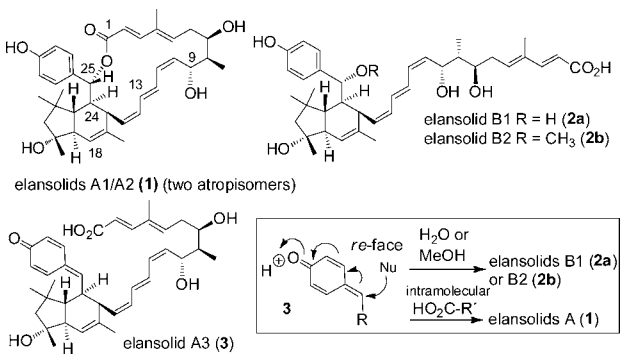


Figure 1. Elansolids A1/A2, B1, B2, and A3 (**1**, **2a**–**c**, **3**).

We proposed a plausible biosynthesis that was based on genetic analysis and preliminary synthetic model studies. The rare *p*-quinone methide moiety in elansolid A3 (**3**) plays a key role for the formation of all other elansolid members. Water or methanol can add to the *re* face of the *p*-quinone methide moiety in elansolid A3 (**3**) and subsequently yield the elansolids B1 (**2a**) and B2 (**2b**). We provided evidence that the remarkable bicyclo[4.3.0]nonane unit is formed by a unique intramolecular Diels–Alder cycloaddition (IMDA), in which the acyclic *p*-quinone methide intermediate engages the diene system.[4]

Herein, we report on the first total synthesis of one of the elansolids, elansolid B1 (**2a**). We devised a convergent strategy that lays the foundation for further studies involving the synthesis of derivatives and exploring the biosynthesis of this unique natural product family. Our synthetic strategy follows one key feature of elansolid biosynthesis, the IMDA, and provides further details on the unique reactivity of the C25 carbinol carbon. Nucleophilic additions to *p*-quinone methides have been previously reported;[5] however, they have never been demonstrated in such a complex context, and in the present setting we reveal a unique case where such a reactive intermediate is sterically stabilized and the stereoelectronic effects that govern its reactivity. This has consequences for biosynthesis and for the further development of reactions that involve *p*-quinone methides.

Retrosynthetically, we envisioned dissecting **2a** into the western and eastern fragments, which could be joined through a linchpin fragment **5**. Substrate **4** could be accessed through a biomimetic Diels–Alder reaction of linear precursor **7**. Controlling the stereochemistry of the olefins should directly

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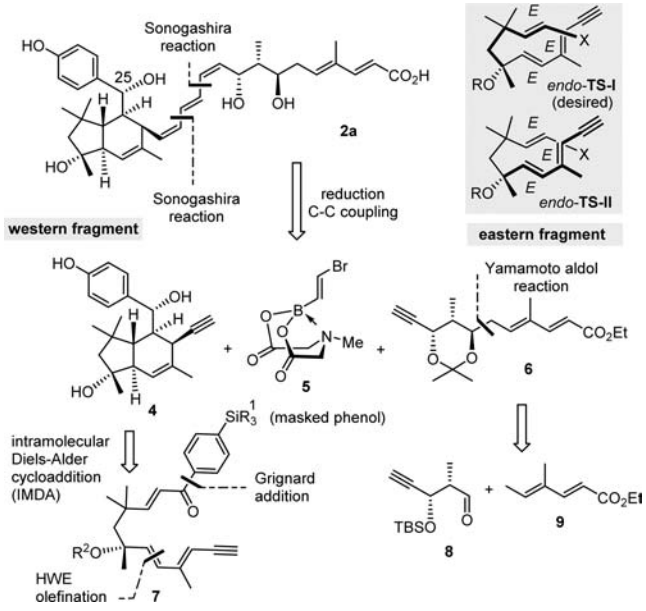
yield the correct relative stereochemistry found in **4**. We anticipated that the desired facial selectivity would be directed by the C20 stereocenter.[6] Interestingly, this stereocenter is proposed to be introduced at the very end of the biosynthesis, and thus the stereoselective outcome at the outset was unknown. Modeling suggested that the correct facial selectivity could be achieved through the more favorable *endo* transition state TS-I (Scheme 1).[7] The eastern fragment **6** could be further disconnected via a convergent vinylogous Yamamoto aldol reaction to give fragments **8** and **9**.[8−10]

Scheme 1. Retrosynthetic Strategy and Proposed *endo* Transition States for the IMDA Cycloaddition



The starting point for this synthesis began with the synthesis of allyl alcohol **10**, prepared as described before.[4] The alcohol was converted to the corresponding aldehyde,[11] and we introduced an aryl group bearing a benzyldimethylsilyl group, which would then be unveiled as the phenol.[12] This was best achieved by trapping of the intermediate aldehyde with the aryl Grignard reagent **11** to give a mixture of allylbenzyl alcohols **12** (dr 1:1). A second oxidation provided the enone, which in the presence of the mild Lewis acid $MgBr_2{\cdot}OEt_2$ directly yielded the desired IMDA product **13** via TS-I (Scheme 1) with excellent endoselectivity in favor of the desired diastereomer (dr ∼30:1). Subsequent cleavage of the PMB-ether provided **14**.

The stereoselective reduction of the keto group turned out to be troublesome. Common reducing agents such as $NaBH_4$ and $LiBH_4$ exclusively provided (25*S*)-epimer **15**, resulting from hydride transfer from the *re* face of the carbonyl group, which was unequivocally proven by an X-ray crystallographic analysis with the phenol **15**.[13] Other efforts to reduce ketone **13**, such as dibal-H, CBS-reduction,[14] glucofuranoside-borane complexes,[15] and the Mandyphos Ir complex,[16] left the starting material untouched. Only $LiAlH_4$ prefentially gave the separable (25*R*) epimer **4** (dr 3:1).[13]

Molecular models indicate that the ketone **14** adopts a conformation similar to that of the *p*-quinone methide moiety in the simplified elansolid A3 model (**20**). In both cases the aryl group is preferentially in a conformation anti to the pseudoaxial alkynyl substituent. The two geminal methyl groups at C-22 block the *si* face so that the *re* face is exposed to attack of nucleophiles. This facial differentiation consequently results in the wrong absolute configuration of the carbinol when hydride serves as nucleophile. Hence we attempted to invert the stereochemistry at C25 by Mitsunobu reaction on the (25*S*) isomer **17** (prepared as single isomer from **15** by $LiBH_4$ reduction) with no success. On the basis of our biosynthetic considerations[2,4] we pursued an alternative approach to invert the stereochemistry that relied on the formation of the *p*-quinone methide **19**, which could be generated from (25*S*)-configured phenol **18**.[17]

We tried to activate the acyl and phenol groups in **18** under acidic or basic conditions, respectively. Once the *p*-quinone methide was generated, *re* face attack of water would create the correct (25*R*) configuration. However, we were unable to convert (25*S*) **18** into the (25*R*) epimer under basic, acidic, or high pressure conditions (Figure 2). Apparently, for steric

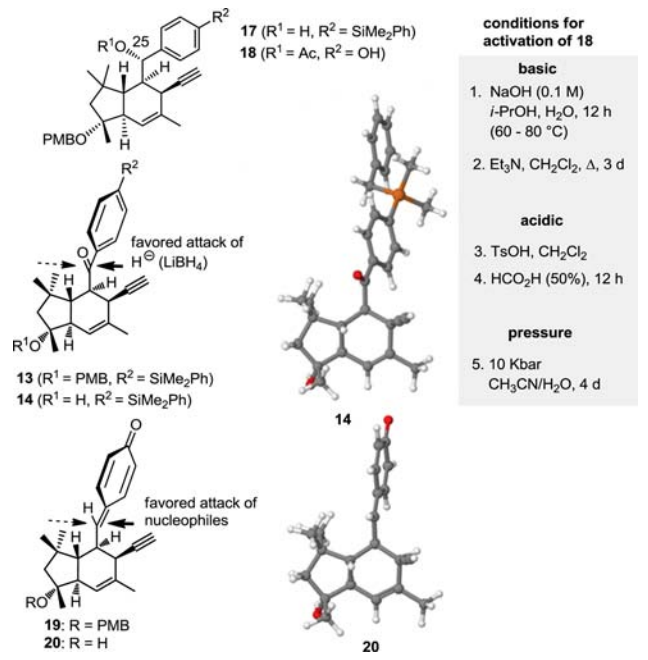


Figure 2. Efforts to selectively prepare the (25*R*) isomer from (25*S*) tetrahydroindanes **17** and **18**, respectively; 3D models of ketone **14** and methide quinone **20**, rationalizing the *re* facial selectivities of nucleophiles at C-25.

reasons, the acetate leaving group cannot adopt a coplanar orientation to the aromatic π-system, a stereoelectronic requirement necessary for facile quinone methide formation. In contrast the (25*R*) epimer **4** can be activated, to smoothly yield the methoxy derivative **16** (dr ∼3:1) when exposed to mildly acidic conditions in methanol (Scheme 2). It is noteworthy that the diastereomeric ratio is lower after methanol addition to the *p*-quinone methide intermediate **20** as compared to the analogous reactions of nucleophiles with elansolid A3 (**3**).[2,3]

The total synthesis was finalized by C_2-extension utilizing a Sonogashira−Hagihara coupling of known alkyne **7**[10] with the MIDA-boronic ester **5**.[18−20] The boronate was then transformed into the vinyl iodide **21** in a straightforward manner (Scheme 3). The second Sonogashira−Hagihara reaction between alkyne **4** and vinyl iodide **21** also proceeded smoothly

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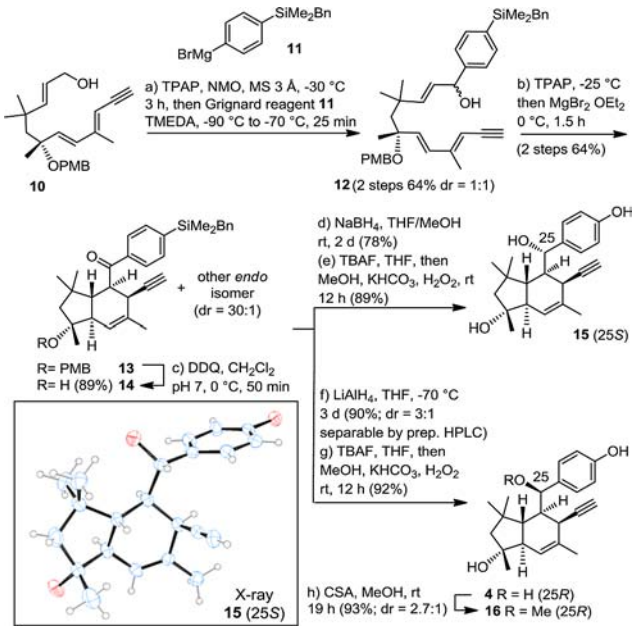
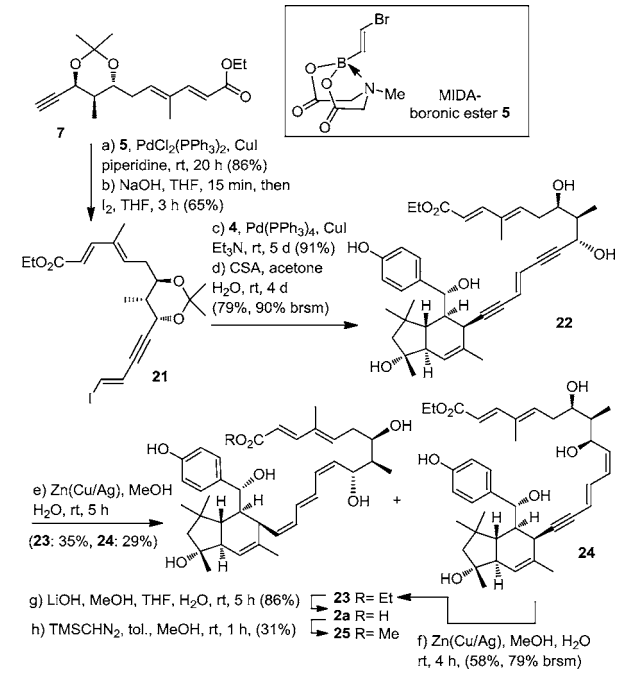
Scheme 2. Preparation of Western Fragment 4

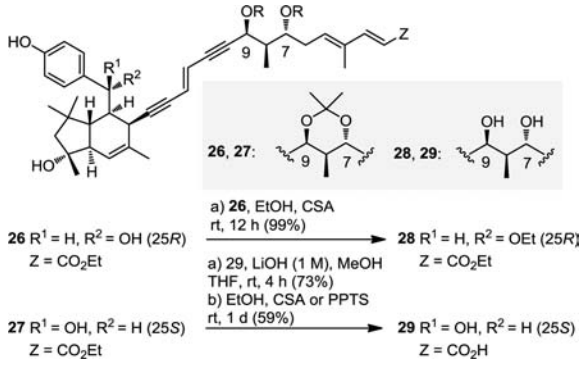


Scheme 3. End Game of Elansolid B1 (2a) Synthesis



so that acetonide removal under mild acid and aqueous conditions provided ene-diyne **22**. Aqueous conditions were crucial to avoid side reactions of the *p*-quinone methide intermediate that forms under acidic condition (see Scheme 4). As expected, selective reduction of the alkynes proved to be challenging.[21] Use of the Lindlar catalyst failed because the olefinic double bonds at C2−C5 were reduced prior to the sterically more hindered alkyne at C-14−C-15. Other standard methods such as 2-nitrobenzenesulfonyl hydrazide[22] (NBSH) or copper-NHC catalyzed reductions[23] were also unsatisfactory. The alloy Zn(Cu/Ag) was the first reagent system that promoted the desired transformation. At elevated temperatures we mainly isolated products in which also the C2−C5 diene

Scheme 4. Trapping the Quinone Methide by Attack of the Nucleophilic Solvent



unit was reduced while only one of the two alkynes were hydrogenated. Optimization of metal alloy preparation[13,24] was crucial to obtain full conversion at room temperature. Selective hydrogenation yield *Z-E-Z* triene **23** and the monohydrogenated yne-diene **24** without affecting the C2−C5 diene system. Compound **24** was resubjected to the reduction conditions to provide **23**. Finally, saponification of the ester group provided elansolid B1 (**2a**).[25] Comparison of the ^{1}H and ^{13}C NMR data (d_6-DMSO) with those of the authentic natural product showed a few deviations (^{1}H: 2H, 3H, 5H; ^{13}C: C1−C5), which was not the case in d_6-acetone. We had encountered these deviations before, during the purification of carboxylates by HPLC.[1b] It is likely due to the formation of an ammonium salt.

The structure of synthetic elansolid B1 (**2a**) was unequivocally secured after preparation of methyl ester **25**, which showed NMR data (δ, J) identical to that of the authentic sample (obtained from the natural source).[1b]

At this stage we were able to prove that the stereochemistry and conformation around C25 plays a crucial role for *p*-quinone methide formation in elansolids (see **4** → **20** in Figure 2). Likewise, the two 25-epimers, **25** and **26**,[26] also show this unique difference in reactivity (Scheme 4). Removal of the acetonide group in (25*R*)-**25** under acidic conditions in ethanol proceeded smoothly but exclusively yielded the (25*R*) configured ethoxy product **28**. Thus, the *p*-quinone methide intermediate is formed and is trapped by ethanol with total stereocontrol. When the (25*S*) alcohol **27** was subjected to the same cleavage conditions, only deprotection of the acetonide took place while the benzyl alcohol at C25 remained untouched.

In conclusion, we accomplished the first total synthesis of a member of the elansolid family, elansolid B1 (**2a**). The synthesis is based on a biomimetic and highly stereoselective intramolecular Diels−Alder cycloaddition. Metal-catalyzed C−C bond formations served to assemble the precursor for the *Z-E-Z* triene unit. We also revealed the stereoelectronic effects governing the remarkable reactivity at C25 and unfolding the role of *p*-quinone methide intermediates, information that is highly relevant to elucidate the chemical details of late stage elansolid biosynthesis.

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■ ASSOCIATED CONTENT

Supporting Information

Descriptions of experimental procedures for compounds and analytical characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(17) Preparation of **24a**: (a) **19**, $LiBH_4$, THF, 82%; (b) TBAF, THF, then MeOH, H_2O_2, $KHCO_3$, 91%; (c) Ac_2O, py, DMAP, CH_2Cl_2; 94%; (d) pyrrolidine, 99%.

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(25) HPLC purification: column C18 ISIS-SP; eluent H_2O/50 mM NH_4OAc:MeOH = 65:35 → 55:45).

(26) The 25-epimer **29** was prepared from benzyl alcohol **16** in an analogous fashion as described for (25*R*)-**28**.