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Stereochemical Reassignment of Mehta and Kundu's Spiculoic Acid A Analogue

James E. D. Kirkham, Victor Lee,* and Jack E. Baldwin*

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, U.K.

victor.lee@chem.ox.ac.uk; jack.baldwin@chem.ox.ac.uk

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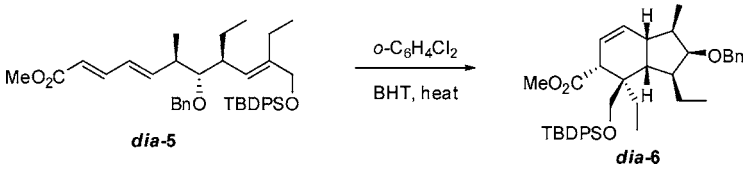
ABSTRACT



A close examination of Mehta and Kundu's synthesis of an analogue of spiculoic acid A revealed discrepancies between their proposed structure and corresponding data. A revised structure is proposed for Mehta and Kundu's analogue after a careful analysis of their key synthetic transformations and published data.

Spiculoic acid A (**1**) is a polyketide natural product recently isolated from the marine sponge *Plakortis angulospiculatus* by Andersen et al.,[1] who proposed that it is biosynthesized via an enzyme-catalyzed intramolecular Diels−Alder reaction.[2] A similar group of natural products were subsequently isolated from the marine sponge *Plakortis zyggompha*.[3] The absolute configuration of spiculoic acid A (**1**) (Figure 1) was previously unknown and was depicted as the enantiomer of **1** in Andersen's original publication. Our group recently completed the biomimetic synthesis of ***ent*-1** and thereby established the absolute configuration of this interesting natural product.[4]

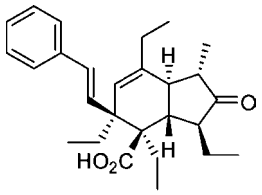


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Figure 1. Natural spiculoic acid A (**1**).

Prior to our publication, Metha and Kundu disclosed their synthetic studies toward spiculoic acid A (***ent*-1**) and prepared a truncated analogue of the natural product.[5] While in the process of reviewing the synthesis of spiculoic acid A (***ent*-1**) and other related compounds, a number of discrepancies in Mehta and Kundu's work came to our attention. We have conducted a thorough assessment of their spectroscopic data and have concluded that the structure proposed by Mehta and Kundu for their analogue (given as **6**) is incorrect. Herein, we present our interpretation and provide a revised structure of this compound.

The key reactions of Mehta and Kundu's synthesis are reproduced, along with the reported NOE correlations of their analogue product, in Scheme 1. Allylic alcohol **2** was subjected to a Sharpless asymmetric epoxidation[6] using D-(−)-diethyl tartrate to apparently give **3**, which was treated with Et_2CuLi[7] to give diol **4**.

(1) Huang, X.-H.; van Soest, R.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2004**, *6*, 75.

(2) (a) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078. (b) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321. (c) Oikawa, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 537.

(3) Berrué, F.; Thomas, O. P.; Fernández, R.; Amade, P. *J. Nat. Prod.* **2005**, *68*, 547.

(4) Kirkham, J. E. D.; Lee, V.; Baldwin, J. E. *Chem. Commun.* **2006**, 2863.

(5) Mehta, G.; Kundu, U. K. *Org. Lett.* **2005**, *7*, 5569.

(6) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

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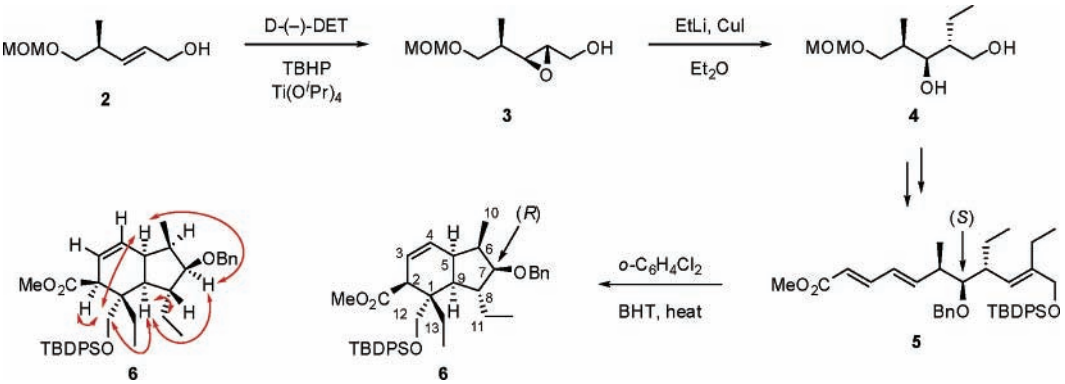
Scheme 1. Synthesis and NOE Interpretation of the Spiculoic Acid A Analogue Product as Presented by Mehta and Kundu[5]



Diol **4** was transformed into precursor **5** via a number of conventional steps, which underwent an intramolecular Diels−Alder reaction upon heating to apparently give spiculoic acid A analogue **6**. The absolute configuration of their analogue product was deduced using NOE correlations based on H-7 as the known reference center (Scheme 1).

A cursory inspection of Mehta and Kundu's publication revealed that the C-7 configuration in analogue **6** is depicted as being (*R*), and the corresponding chiral center in precursor **5** is depicted as being (*S*). Our initial response was that the proposed absolute configuration of analogue **6** was incorrectly assigned due to the erroneous representation of the C-7 reference center. Hence, all their NOE conclusions were invalid. However, on further inspection of Mehta and Kundu's publication, we discovered that the situation is more complicated than first thought.

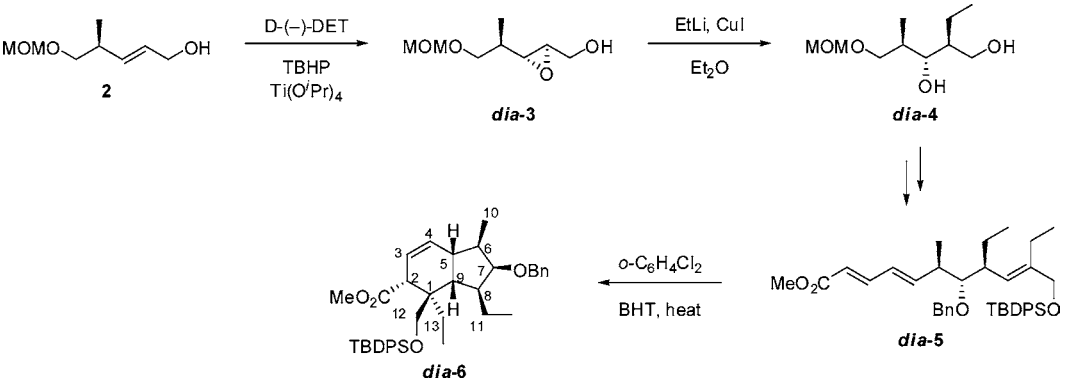
Scheme 2 depicts our analysis of the key chemical steps reported by Mehta and Kundu. The two authors claimed that their Sharpless asymmetric epoxidation of allylic alcohol **2** using D-(−)-diethyl tartrate gave epoxide **3** with the β-configuration indicated in Scheme 1. This is in contradiction to what is predicted by the Sharpless mnemonic model.[6] The correct product of the reaction should be ***dia*-3**, in which the epoxide has the α-configuration indicated in Scheme 2. Indeed, both −OBn and −OTBDPS protected versions of **2** have been epoxidized using D-(−)-diethyl tartrate in the Sharpless epoxidation to deliver the corresponding α-epoxides.[8] Subsequent reaction of Et_2CuLi with epoxide ***dia*-3** should have given ***dia*-4**.[7] Eventually, after the subsequent functional group manipulations and chain extension reactions, the expected product should be ***dia*-5**. The intramolecular Diels−Alder reaction[9] of ***dia*-5** should therefore have delivered ***dia*-6** as the analogue product.

Table 1. ^{1}H Assignment of the Major Signals of ***dia*-6** Recorded in $CDCl_3$

C no.	δ_H	C no.	δ_H
2	3.18, d	8	2.20−2.32, m
3	5.41, ddd	9	2.11, t
4	5.60, dd	10	1.00, d
5	1.95−2.05, m	11	1.30−1.40, m
			1.60−1.80, m
6	1.85−1.95, m	12	3.39, $d_{(1/2)ABq}$
			3.44, $d_{(1/2)ABq}$
7	3.86, t	13	1.60−1.80, m

The absolute configuration of ***dia*-6** was established in the following way. First, we assigned the major ^{1}H chemical shifts to ***dia*-6** (Table 1) on the basis of an analysis of the

Scheme 2. Refined Analysis of Mehta and Kundu's Synthesis of the Spiculoic Acid A Analogue



^{1}H and COSY spectra provided in Mehta and Kundu's Supporting Information.[5,10]

It should be noted that a ^{1}H signal of one of the diastereotopic C-11 protons resonates at δ 1.30−1.40. The ^{1}H signal between δ 1.60 and 1.80 should correspond to the remaining C-11 and C-13 methylene protons. A detailed discussion of the ^{1}H NMR assignment can be found in the Supporting Information.

We then proceeded to examine Mehta and Kundu's NOESY spectrum to establish the correct absolute configuration of their analogue product. Our rationale is presented in a number of NOE diagrams, to illustrate the logic of our deduction.

We observed NOE correlations between H-6 and H-7, H-7 and H-8, and H-6 and H-8 (Figure 2). This was not

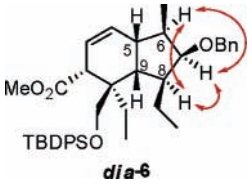


Figure 2. NOE correlations observed between H-6 and H-7, H-7 and H-8, and H-6 and H-8.

surprising, as we predict that all three of these protons should be oriented on the α-face, as dictated by the synthetic transformations involved.

Mehta and Kundu reported observing NOESY correlations between H-7 and H-5 and between H-7 and H-9 (Scheme 1). However, we observed neither of these correlations in their spectrum. Instead, we were able to pinpoint correlations between H-10 and H-5, H-10 and H-9, and H-11 and H-9 (Figure 3). We therefore conclude that both H-5 and H-9

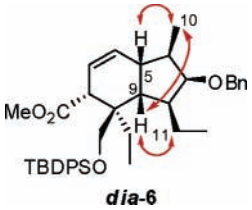


Figure 3. NOE correlations observed between H-10 and H-5, H-10 and H-9, and H-11 and H-9.

are on the β-face and that the ring junction is cis.

Having established the absolute configuration of the ring junction, we then focused our attention on elucidating the stereochemistries of the remaining C-1 and C-2 stereocenters. To this end, NOE correlations were observed between H-12 and H-2, H-12 and H-5, and H-12 and H-9 (Figure 4). These

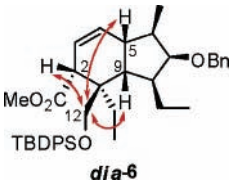


Figure 4. NOE correlations observed between H-12 and H-2, H-12 and H-5, and H-12 and H-9.

are consistent with Mehta and Kundu's observations, and we agreed with their deduction that H-2 and H-12 are both on the same face as H-5 and H-9. However, we conclude that all four substituents are on the β-face, not the α-face.

Additional evidence substantiating our conclusion lies in the observation of NOE correlations between H-4 and H-6 and between H-4 and H-10 (Figure 5). The stronger of these

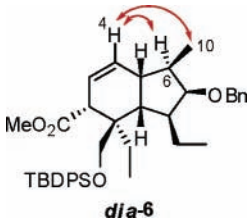


Figure 5. NOE correlations observed between H-4 and H-6 and H-4 and H-10.

correlations is the former, indicating that H-4 is in closer proximity to H-6 than it is to H-10. The "butterfly" shape of the molecule, a result of the cis ring junction, therefore requires that H-5 and H-9 be on the convex β-face. Thereby, H-4 is in closer proximity to H-6 than to H-10.

Further supporting evidence is afforded by an analysis of the four possible anti and syn intramolecular Diels−Alder transition states. Figure 6 illustrates, using simplified triene **7** as a model, that anti and syn transition states would lead to trans and cis C-5/C-9 ring junctions, respectively. The cis ring junction of ***dia*-6** therefore reveals that it must have been formed via a syn transition state. A close inspection of Figure 6 reveals that a syn transition state dictates that both the C-1 substituent and H-2 are not only on the same face but also on the same face as both H-5 and H-9. This supports the observed NOE interactions illustrated in Figure 4. A

(7) (a) Nagaoka, Y.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372.

(8) (a) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768. (b) Williams, D. R.; Jass, P. A.; Tse, H. L. A.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552.

(9) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779.

(10) It should be noted that the stereochemistry of Mehta and Kundu's analogue product given on page 11 of their Supporting Information is inconsistent with that given for **6**.

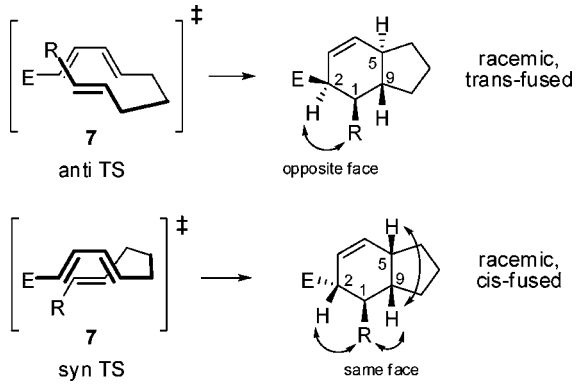


Figure 6. Illustration of the relationship between the Diels−Alder transition state and the resulting relative stereochemistry.

possible theoretical rationale for the formation of diastereoisomer ***dia*-6** can be found in the Supporting Information.

We also considered the possibility that Mehta and Kundu might have synthesized epoxide **3** (Scheme 1) using L-(+)-diethyl tartrate but mistakenly reported the wrong tartrate in their publication. However, we consider this to be highly unlikely. The intramolecular Diels−Alder reaction of compound **5** would have generated compound **8** containing 6*R*, 7*S*, and 8*R* configurations, regardless of the stereochemistries at the remaining chiral centers (Figure 7). Such a structure would be inconsistent with the observed NOE interaction between H-6 and H-8 as they would be on opposite faces of the five-membered ring. In addition, it would be reasonable to expect that an NOE correlation between H-8 and H-10 would be observed in compound **8**. The absence of this correlation implies that Metha and Kundu did not synthesize **8**.

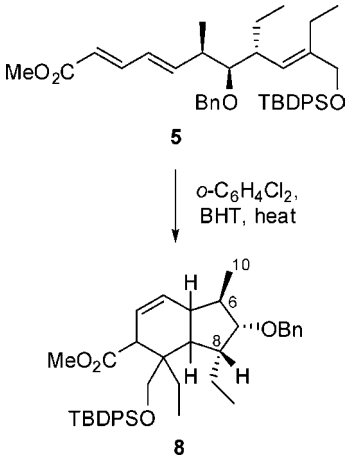


Figure 7. Illustration of the (6*R*,7*S*,8*R*) stereochemistry that would be present in the analogue product if Mehta and Kundu had used L-(+)-diethyl tartrate.

In conclusion, we have conducted a thorough analysis of Mehta and Kundu's synthesis of their spiculoic acid A analogue. The discrepancies uncovered in this exercise have been rationalized and led to a revision of the structure of their Diels−Alder product from **6** to ***dia*-6**.

Acknowledgment. We thank Dr. Timothy Claridge for helpful comments.

Supporting Information Available: A detailed discussion of the ^{1}H NMR assignment and a theoretical rationale for the formation of ***dia*-6** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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