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Permuting Diels-Alder and Robinson Annulation Stereopatterns

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Abstract

Controlled isomerization of the double bond of certain Diels-Alder reactions provides substrates that, upon oxidation, give rise to products whose gross structure corresponds to that of a Robinson annulation. In these cases, the stereochemistry of the Robinson annulation product reflects the fact that the initial combination occurred in a Diels-Alder mode. Using these principles, we have synthesized carissone and cosmoic acid. In the latter case, our total synthesis raised serious questions as to the accuracy of the assigned structure of the natural product.

Introduction

Synthetic planning directed to conjugated octalones, of the type **1**, traditionally tends to center around enolate and enol based progressions inherent in the expression “Robinson Annulation” (RA, see eq. 1).^{1,2,3} By contrast, nonconjugated octalone systems of the type **2** are perceived as likely to arise from a Diels-Alder based cycloaddition logic (DA, eq. 2).^{4,5,6,7}

(1)

(2)

Not surprisingly, these widely used synthetic platforms lead to differing biases in diastereoselection. For instance, consider the consequences of these modalities for orchestrating a 1,4 stereorelationship in a bicyclic product arising from two kinds of cyclohexene substrates – an enolate (**3**) and an enone (**5**). In the R A m o d e , diastereofacial induction tends to be stereoelectronically, rather than sterically, driven for the RA progression.⁸ Thus, if enolate alkylation occurs in the preferred axial sense, with the resident C₅ group (asterisk) equatorial, formation of an “anti product,” of the type **4** would be favored.^{9,10} By contrast, in the DA modality, preferred combination of the DA diene with **5** would tend to occur anti to the R group, leading to a “syn” type product (**6**).¹¹

(3)

(4)

These differing stereopatterns are also associated with strikingly different displays of the key functional groups (olefin and ketone) in the bicyclic products (compare octalones **1** and **2**). Given this situation, we addressed the question as to whether the conventional structural and diastereoselection tendencies can be exploited such that a DA “stereopattern” might be transmitted to a typical RA type product.

Recently, we described a somewhat fortuitous discovery, wherein the double bond of a Diels-Alder derived octalone of the type **7** can be isomerized under mediation by silica gel to afford **8** (Scheme 1).^{12,13} The latter type of structure is easily seen to be a double bond isomer of a standard Diels-Alder cycloaddition product. It could well be anticipated that Saegusa-Ito-type oxidation^{14,15} of **8** would give rise to **9**, in which a DA stereochemical pattern is ensconced in an RA functional group arrangement (i.e. the expected “wild-type” RA stereomotif would be that shown in **10**).

Attention has already been drawn¹⁶ to the potential value of pattern recognition analysis (PRA) as a resource in the planning of the synthesis of complex targets. While the compelling logic of prioritized strategic bond disconnection, advanced by Corey and associates many years ago,^{17,18} still lies at the heart of contemporary retrosynthetic analysis, PRA, which seeks out identifiable holistic substructural domains, may provide a complementary venue for forward planning.¹⁶ Thus, the question we posed above, concerning the permutability of the diastereoselectivity biases of these key reaction types, has the potential to offer new avenues for synthetic planning, particularly in subtle issues of stereochemistry (vide infra, syntheses of carissone¹⁹ and of the reported structure of cosmoic acid²⁰).

Results and Discussion

As shown in Scheme 2, we began our inquiry by demonstrating how two mainstay products of classical RA-based strategies, the Hajos–Parrish ketone (**13**)²¹ and the Wieland–Miescher ketone (**14**),²² could be synthesized in quite reasonable overall yields from the easily available, appropriate α -methylcyclohexenones.^{23,24} Of course, in the particular cases of **13** and **14**, there were no issues of relative stereochemistry to be addressed. Though we have not yet pursued the matter, enantioselectivity could, in principle, be realized from a catalyst that can impose absolute stereochemical guidance at the stage of the [4+2] cycloaddition event.

We next turned to cases bearing C₄ substitution on the dienophilic cyclohexenone substrate. As shown in Scheme 3, the facial stereoselection of the cycloaddition reaction is high (>10:1).²⁵ At this writing, the ratio of $\Delta^2:\Delta^3$ regioisomers in the double bond migration step in this series was somewhat disappointing.^{26,27} While the precise factors governing the selectivity of isomerization remain to be determined, they may well reflect minimization of peri interactions between C₄ and C₆ in the isomerized structure. Fortunately, we were able to retrieve the un-rearranged material and re-subject it to isomerization, thus improving our material throughput. Saegusa-Ito oxidation^{14,15} proceeded well to afford **17a** and **18**, respectively. That epimerization had not occurred at C₆ during this step, was shown in the case of **17a** by its non-identity with compound **17b**, previously described and assigned in a rigorous way by Grieco and co-workers.^{28,29} Subjection of compound **17a** to equilibrating conditions did, indeed, lead to epimerization, with emergence of **17b**. Thus, the chemistry described above does lead to the otherwise difficultly accessible 6-axially alkylated Δ^4 3-octalones.

This chemistry was next extended to a situation where the substituent on the cyclohexenone dienophile appears at C₅. Four cases were examined (Table 1). As seen, the cycloadditions were, again, highly stereoselective, providing substantially one isomer in the Diels-Alder reaction.²⁵ Again, silica gel mediation of the double bond isomerization occurred quite smoothly, this time in higher ratios than those contained in the 4-substituted series. Once again, Saegusa-Ito oxidations^{14,15} delivered the target octalones, this time bearing a substituent at C₇,²⁶ *cis* to the junction methyl group. This type of series is not readily generated from classical Robinson annulation strategies.

Adding to the patterns accessible by this logic was the fact that the chemistry is also extendable to the situation where the Diels-Alder diene contains a methyl substituent group at a terminal carbon³⁰ (Table 2). Once again, the levels of face selectivity in the cycloadditions were excellent, giving rise to the major adducts shown. Silica gel mediated isomerizations afforded the “iso-DA-type” products in high ratios relative to starting DA adducts. Following Saegusa oxidation, there were obtained the octalones **33**, **35**, and **37** with a *cis* relationship between the junction (C₁₀) and the C₆ or C₇ substituents.²⁶ As discussed above, this stereopattern is not readily obtained from Robinson annulation strategies, either due to epimerization, in the case of the 6-substituted product, or because of the stereoelectronics of alkylation which govern the case where the substituent is at C₇.

The applicability of this permuting of RA:DA logic was demonstrated in the context of two total synthesis programs. As will be seen, the targets were selected to exemplify the enhanced possibilities enabled by the chemistry described above. It was for the purpose of synthesizing the sesquiterpene carissone that we conducted the Diels-Alder reaction of **38** with **19**.^{19,31} As shown in Table 2, cycloaddition of **38** and **19** gave rise to a cycloadduct which underwent silica induced double bond isomerization, followed by Saegusa oxidation¹⁴ to afford **35**. Not surprisingly,³² selective reduction of the non-conjugated ketone (C₉) could readily be achieved to afford an alcohol (**39**), which, upon Barton deoxygenation,³³ gave rise to **40**. Deprotection, as shown, afforded (+)-carissone (**41**). We note that an elegant total synthesis of (+)-carissone, that does not draw from the chiral pool, has recently been described by Stoltz and colleagues.³⁴ In the Stoltz synthesis, the C₇–C₁₀ stereorelationship was also managed through a non-RA program.

Recently, we noted a disclosure in the literature describing the isolation of a compound called cosmoic acid (**42**)²⁰ from *Cosmos sulphureus*, a plant native to Brazil and Mexico. This plant had been identified as a source of anti-malarial natural products, although antimalarial properties of **42**, per se, were not reported. The gross structure and stereochemistry of cosmoic acid had been determined strictly by spectroscopic methods,

not supported by any degradative or crystallographic investigations.²⁰ Given the Pattern Recognition Analysis line of thinking,¹⁶ one immediately notes the “iso-Diels-Alder” characteristic of cosmoic acid.³⁵ In this context, C₃ of the C₃–C₄ iso-DA pattern carries a carboxyl group. One might well have considered synthesizing cosmoic acid by a Diels-Alder reaction of diene **43**³⁶ with the generic dienophile **44**, followed by isomerization of **45**. To us, it seemed that such a program presented unlikely prospects for success. First, dienes of the type **43** tend to be quite unstable.³⁷ Furthermore, the electron withdrawing carboxyl group at C₂ would render this diene even less reactive in a hypothesized DA cycloaddition^{4–6} with an electron withdrawing dienophile of the type **44**. Moreover, the key silica gel-mediated isomerization reaction has not been demonstrated in the context of octalin-related DA adducts arising from cycloadducts of the type **45**. Instead, we preferred to resort to our usual 2-siloxybutadiene DA building block. If cycloaddition and isomerization would occur with appropriate selectivities, success would depend on converting the subsequently tautomerized ene-siloxy function in **47** to the corresponding unsaturated acid.

In the event, reaction of siloxydiene **46**³⁸ with the enone **44**³⁹ occurred quite smoothly in the presence EtAlCl₂ to provide **49** in 90% yield. Happily, the silica gel-mediated isomerization of **49** proceeded, providing the isomerized silylenol ether (see **47**). It seemed prudent to protect the ketone in the light of subsequent operations which were planned (*vide infra*). Remarkably, it was possible to convert the ketone function of **47** to its corresponding enol ether derivative, **50**, via deprotonation with LDA and O-methylation with dimethyl sulfate. This method is not a common one for generating methyl enol ethers from ketones and could warrant future research as to its scope.

With compound **50** in hand, we turned to the conversion of the silylenol ether to the corresponding vinyl triflate. In the event, this subgoal was accomplished by generating the corresponding site-specific enolate via the action of **50** with methyllithium,⁴⁰ whereupon quenching with the Comins reagent⁴¹ afforded the corresponding vinyl triflate **51**. With compound **51** in hand, we examined the possibility of a modified Heck-carbonylation.⁴² Happily, this subgoal was accomplished relatively smoothly (75% yield) under the conditions shown. The intermediate acid was converted to its methyl ester **52**. Hydrolysis of the enol ether function gave rise to ketone **53** in an overall yield of 75%. Saponification of the methyl ester gave rise to a product, tentatively assigned as structure **42**.

Surprisingly, the NMR spectrum of presumed **42**, thus obtained, exhibited certain clear differences from the NMR spectrum reported for cosmoic acid.⁴³ Obviously, we had reason to be concerned about a possible structural mis-assignment on our part, somewhere during our synthetic work. Upon reexamination of the intermediates generated in the total synthesis progression and our assignments along the way, we remained convinced that we had in fact synthesized **42** as shown. Happily, the matter was objectively established by an X-ray crystal structure of the synthetic material, which clearly revealed the end product of our total synthesis to be compound **42**.⁴⁴ At this stage, it seemed very likely that the structure of the natural product cosmoic acid does not correspond to that shown in **42**. Several attempts were made to network with the original authors,²⁰ but these efforts did not provide any additional insight. No helpful samples or spectral readouts were obtained.

At the time of writing, we can only conclude that the structure of cosmoic acid does not correspond to **42**. Having no access to the natural product, itself, we are unable to provide an informed opinion as to the correct structure of naturally occurring cosmoic acid.

Finally, we examined substitutions at C₆ of the cyclohexenone (which would correspond to C₈ of the resulting octalone²⁶). In this connection we studied the case of compound **54**.⁴⁵ Attempted cycloadditions of **54** with diene **46** resulted in approximately 1:1 mixtures.⁴⁶

Thus, the stereoguidance that we had successfully encountered in the cases of the 4- and 5-substituted 2-methylcyclohexenones, apparently does not provide useful margins with the 6-substituted system (cf. **54**).²⁵ This, in itself, is perhaps not surprising in the light of the nature of the Diels-Alder reaction.⁴⁻⁶ In the cycloaddition of a compound such as **54**, one envisions the initial orienting bonding would occur at C₃ of the cyclohexenone, and slightly later at C₂ in the imperfectly concerted cycloaddition. That being the case, the methyl group at C₆ would be only weakly directing, since it is in a 1,4-relationship to the emerging “lead” bond.

Conclusion

In summary, we have demonstrated modalities for permuting the stereochemistry and gross structural patterns emerging from a classical Robinson annulation (RA), with Diels-Alder (DA)-based technologies. The line of reasoning has led to stereospecific syntheses of carissone and the previously assigned structure of cosmosoic acid. In the latter case, the total synthesis work suggests that the structural assignment of the natural product is in error. We are hopeful that the successful demonstrations provided above for broadening the accessible relationships applicable to PRA can be applied to interchanging the structural and stereomotifs of other reaction dualities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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27. In several instances, it was shown that the ratios of the $\Delta^2:\Delta^3$ silyl enol ether isomers were virtually the same when we started with either of the components. Thus, it seems likely that we are generating substantially an equilibrium mixture. We also note that favoring of $\Delta^2:\Delta^3$ isomer in these *cis*-fused compounds correlates well with the enolization tendencies of *cis*-fused decalones.
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Scheme 1.
Diels-Alder/isomerization sequence.

Scheme 2.

Synthesis of Hajos–Parrish ketone (**13**) and Wieland–Miescher ketone (**14**).^a

^aKey: (a) EtAlCl₂, CH₂Cl₂, 0 °C → RT; (b) silica gel, 110 °C, toluene; (c) Pd(OAc)₂.

*Isomerization ratio.

Scheme 3.C₄-Substituted dienophiles.^a

^aKey: (a) EtAlCl₂, CH₂Cl₂, 0 °C → RT; (b) silica gel, 110 °C, toluene; (c) **17a**: Pd(OAc)₂; (d) **18**: DDQ, DTBMP. *Isomerization ratio.

Scheme 4.

Total synthesis of (+)-carissone.

^aKey: (a) EtAlCl₂, CH₂Cl₂, 0 °C → RT; (b) silica gel, 110 °C, toluene, 94% yield, 15:1 isomerization ratio; (c) Pd(OAc)₂, 79% yield; (d) NaBH₄, EtOH, 0 °C, 95% yield; (e) TCDI, DMAP, toluene; then AIBN, Bu₃SnH, 65% yield; (f) BrBMe₂, DCM, −78 °C, 90%.

Scheme 5.
Synthetic strategy toward cosmoic acid.

Scheme 6. Synthesis of **42**.

^aKey: (a) EtAlCl₂, CH₂Cl₂, 0 °C → RT, 90% yield, (b) silica gel, 110 °C, toluene, 85% yield, 5:1 isomerization ratio, (c) LDA, Me₂SO₄, THF, -78 °C, 80% yield, (d) MeLi, PhNTf₂, THF, 88% yield, (e) Pd(OAc)₂, PPh₃, Et₃N, CO balloon, MeOH/DMF, (f) 1 N HCl, two steps 75% yield, (g) LiOH, THF/H₂O, 95% yield.

^aKey: (a) EtAlCl_2 , CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{RT}$, 82%.

Scheme 7.

DA of 6-Substituted Diene Systems.

^aKey: (a) EtAlCl_2 , CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{RT}$, 82%.

Table 1

C5-Substituted dienophiles.

Reaction scheme: A C5-substituted dienophile (RO-CH=CH-C(=O)-R') reacts with a maleic anhydride derivative (R''-C(=O)-CH=CH-C(=O)-R'') under conditions (a, b) to form an isomerized adduct. The adduct is then oxidized under conditions (c or d) to form an enone.

entry	dienophile	isomerized adduct	enone
1			
2			
3			
4			

^aKey: (a) EtAlCl₂, CH₂Cl₂, 0 °C → RT; (b) silica gel, 110 °C, toluene; (c) Pd(OAc)₂; (d) DDQ, DTBMP.

* Isomerization ratio.

Table 2

Substituted diene.

entry	dienophile	isomerized adduct	enone
1		 32 , 85%, 10:1*	 33 , 82%
2	 19	 34 , 94%, 15:1*	 35 , 79%
3	 31	 36 , 81%, 12:1*	 37 , 58%

^aKey: (a) EtAlCl₂, CH₂Cl₂, 0 °C → RT; (b) silica gel, 110 °C, toluene; (c) Pd(OAc)₂.

* Isomerization ratio.