Reversal of facial selectivity in complex Diels–Alder reactions†

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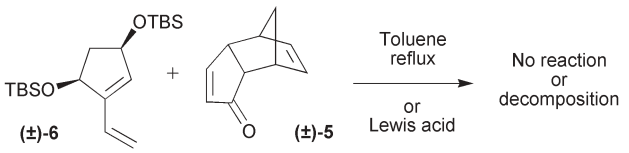
A complex Diels–Alder reaction between a semi-cyclic diene with allylic silyloxy substituents and a bromo enone presented an unusual diastereoselectivity: attack of the diene occured on its more hindered face, and this reversal of selectivity was shown to be induced by the presence of a bromo substituent in the dienophile.

In the course of our studies toward the synthesis of FR182877, we explored a route involving a complex intermolecular Diels–Alder reaction to construct the ABC tricycle. This compound, isolated in 1998 from *Streptomyces* sp. No. 9885 by Sato and coworkers,[1] has a mode of action similar to that of taxol, which makes it a potential antitumor drug.[2] Total syntheses of (+)-FR182877 and the natural (−)-enantiomer have been reported by Sorensen *et al.*[3] and Evans and Starr,[4] respectively, and synthetic approaches have been published by several groups.[5]

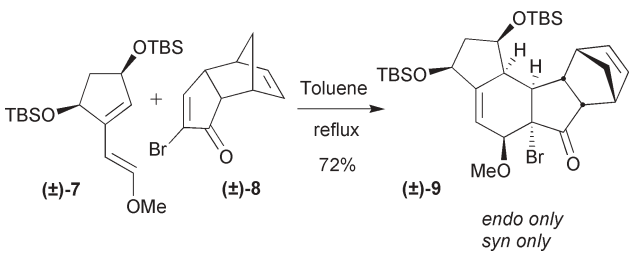
The retrosynthesis we envisioned for the ABC tricycle is shown in Scheme 1. Compound **1** would be formed by an olefin migration from **2**. The latter would be synthesized from diene **4** and dienophile **5** by a Diels–Alder/retro Diels–Alder sequence *via* adduct **3**. A similar reaction has been reported by Takano *et al.* for the synthesis of estrone:[6] in the presence of a Lewis acid, the *exo* product is obtained exclusively, which corresponds to the desired stereochemistry for compound **3**.

We first studied the key Diels–Alder coupling between racemic enone (±)-**5**[7] and (±)-**6**, a racemic model of diene **4** (X = H, R = TBS) lacking the methyl substituent between the two protected alcohol functions (Scheme 2).‡ No reaction was observed under thermal conditions, and numerous Lewis acids were tested without any success.§

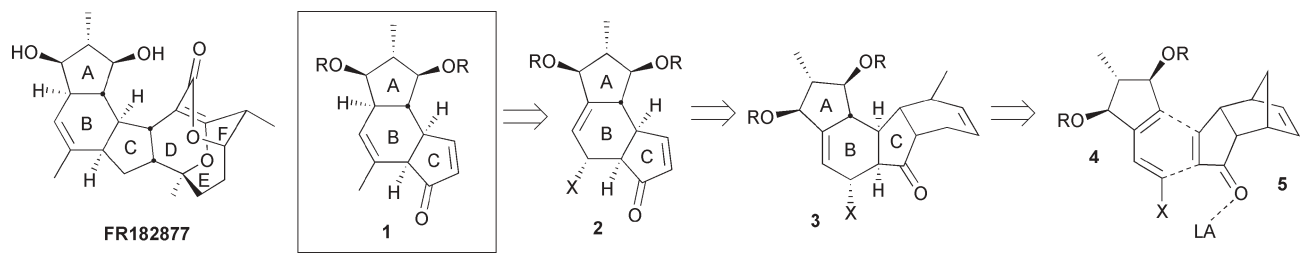


Scheme 2 First attempts of Diels–Alder reactions.

After extensive experimentation, it was found necessary to promote the reactivity of both diene and dienophile in order to obtain good conversions in the Diels–Alder reaction. *E*-Diene (±)-**7** (X = OMe) gave the best results, and enone (±)-**8**,[8] which possesses an α-bromo substituent,[9] was chosen because it was easily accessible from enone (±)-**5**. When these two partners were heated in toluene at reflux for 40 h, the reaction proceeded in high yield (Scheme 3), with total regioselectivity and diastereoselectivity. Careful purification of the starting materials and exclusion of oxygen during the reaction must be effected to prevent aromatization of the newly formed six-membered ring. Use of Et_2AlCl at −78 °C gave the same product, but in only 27% yield (52% based on recovered enone (±)-**8**).



Scheme 3 Diels–Alder reaction between activated substrates.



Scheme 1 Retrosynthesis of the ABC tricycle of FR182877.

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† Electronic supplementary information (ESI) available: General considerations; syntheses and characterization of compounds (±)-**9**, (±)-**9a**, (±)-**12**, (±)-**13**, (±)-**15–17**, *anti* and *syn* (±)-**18**; crystal structure data for (±)-**9a** and (±)-**12**. Inquiries about crystallographic data should be addressed to Louis Ricard. See http://dx.doi.org/10.1039/b509041e

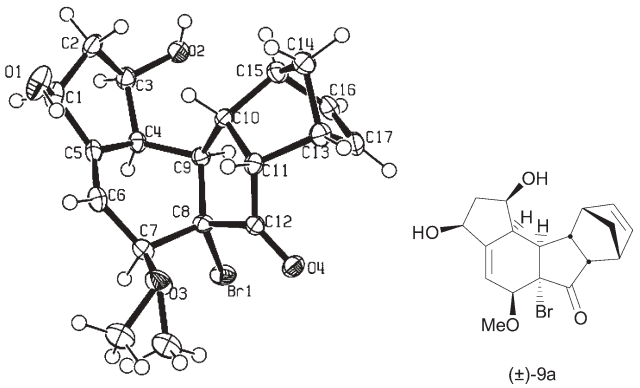
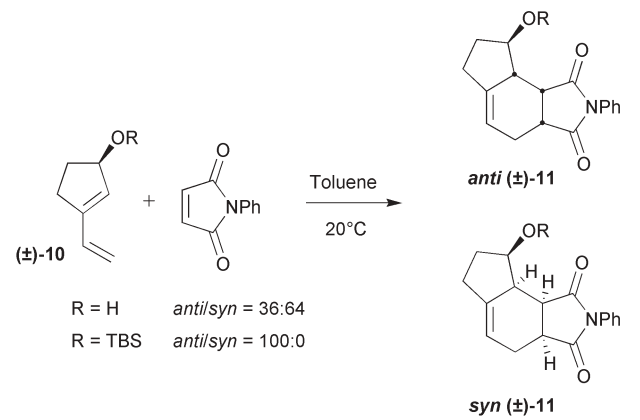


Fig. 1 Solid state structure of (±)-**9a**.

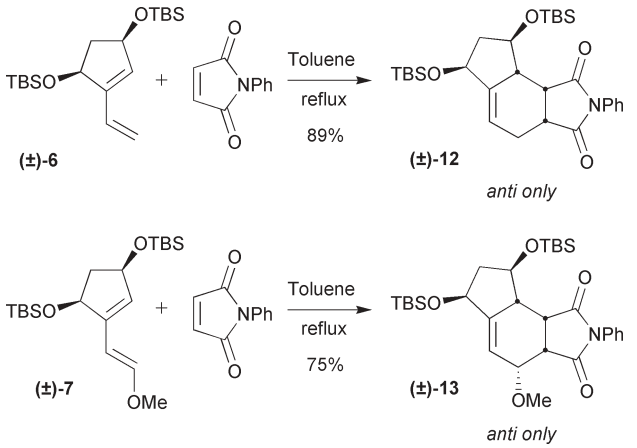
The stereochemistry of (±)-**9** was determined by X-ray analysis of a crystalline derivative, diol (±)-**9a** (Fig. 1),¶ obtained by treatment with HF in acetonitrile. The Diels–Alder reaction proceeds *via* an *endo* transition state exclusively, and there is a very strong facial bias for both partners. Enone (±)-**8** reacted from the bridge-head side, which was expected, but attack of diene (±)-**7** occurred *syn* to the OTBS substituents: diene (±)-**7** was thus approached on its more hindered side. When the alcohol substituents were protected as TIPS (triisopropylsilyl) ethers, the same diasteroselectivity was observed, which is even more surprising in view of the bulkiness of these protecting groups.

This totally unexpected facial selectivity has no precedent in the literature.[10] To our knowledge, the only case of *syn* attack of such semi-cyclic dienes in Diels–Alder reactions was observed by Overman *et al.* for an allylic alcohol substituent (Scheme 4, R = H), where the facial selectivity can be explained by a hydrogen bond between the diene and dienophile in the transition state.[11] However, when the alcohol is protected as a TBS ether (Scheme 4, R = TBS), the expected product *anti* (±)-**11** is obtained exclusively.

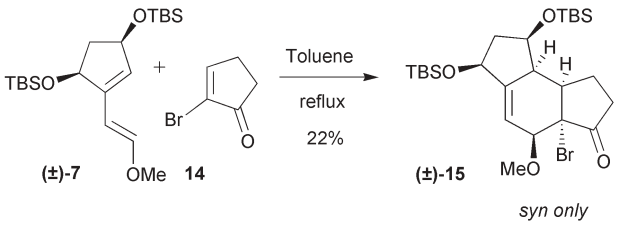
In order to explain the reversal of facial selectivity of diene (±)-**7**, we first tried to assess the effect of the methoxy substituent of the diene. Reaction of dienes (±)-**6** and (±)-**7** with *N*-phenylmaleimide gave the expected *anti* adducts (Scheme 5).‖ Both these dienes behaved according to Overman's precedent, indicating the lack of influence of the methoxy group alone.



Scheme 4 Overman's precedents.



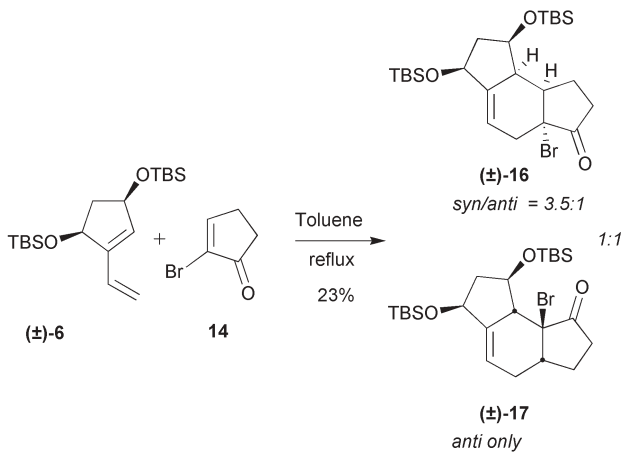
Scheme 5 Diels–Alder reactions with *N*-phenylmaleimide.



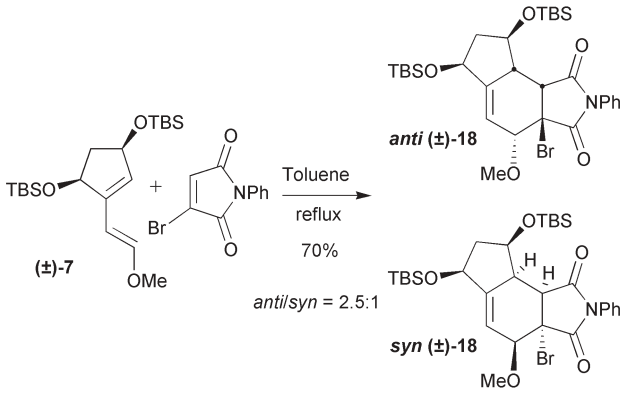
Scheme 6 Diels–Alder reaction of diene (±)-**7** with a simple bromo enone.

We then reacted diene (±)-**7** with a simple dienophile, α-bromocyclopentenone **14** (Scheme 6). The *syn* adduct (±)-**15** was produced exclusively.** Since enones (±)-**8** (Scheme 3) and **14** lead to the same facial selectivity in the Diels–Alder reaction with (±)-**7**, we can assume that the bridged structure does not participate in this unusual selectivity. On the other hand, the opposite stereochemistry of compound (±)-**13** (Scheme 5) *versus* compound (±)-**15** (Scheme 6) seems to be due to the bromo substituent.

In order to verify this assumption, compounds (±)-**6** and **14** were heated in toluene at reflux. The conversion was poor, but the reaction very clean, giving two regioisomeric adducts (Scheme 7).



Scheme 7 Diels–Alder reaction of diene (±)-**6** with a simple bromo enone.



Scheme 8 Diels–Alder reaction with *N*-phenylbromomaleimide.

The desired regioisomer (±)-**16** was obtained with mainly the *syn* stereochemistry, but the other regioisomer resulted from the *anti* attack.††

Finally, diene (±)-**7** was reacted with *N*-phenylbromomaleimide (Scheme 8). In this case, the reversal of selectivity is not total (compare with the formation of (±)-**13**, Scheme 5), but a substantial amount of the *syn* diastereomer (30%) is formed, proving once again the role of the bromo substituent in the stereochemical course of this Diels–Alder reaction.

From the previous experiments, we can deduce that the bromo substituent of the dienophile induces the reversal of the facial selectivity of dienes (±)-**6** and (±)-**7**. If this effect is due to an electrostatic interaction in the Diels–Alder transition state between this bromo substituent and the silicon atoms of one or both TBS protecting groups, this interaction should be disrupted in a polar solvent.‡‡ However, we could not verify this hypothesis since diene (±)-**7** decomposes when heated in the presence of (±)-**8** in THF, DMF or dioxane. Other protecting groups for the diol moiety, non silicon-based, were also investigated: analogues of diene (±)-**7**, bearing two methyl or benzyl ethers, have been prepared. Unfortunately, the Diels–Alder adducts resulting from reactions of these compounds with (±)-**8** degraded very rapidly, so no information could be gained from these additional experiments.

In summary, we have discovered an intriguing reversal of selectivity in a Diels–Alder reaction between a semi-cyclic diene bearing allylic silyloxy substituents and bromo enones. The importance of the bromo substituent, which directs the attack of the dienophile to the more hindered face of the diene, has been proven. Further work to explain this directing effect is currently in progress in our laboratory.

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Notes and references

‡ Preparation of model dienes (±)-**6** and (±)-**7** will be reported elsewhere. For the synthesis of dienes **4** (X = H, R = TBS or Bn), see: J.-A. Funel and J. Prunet, *J. Org. Chem.*, 2004, **69**, 4555–4558.

§ No reaction occurred with $EtAlCl_2$, $LiClO_4$ and $ZnCl_2$, Et_2AlCl only hydrolyzed the TBS ethers, and degradation was observed in the presence of $AlCl_3$, $BF_3{\cdot}OEt_2$ and $SnCl_4$.

¶ Crystal data for (±)-**9a**: $C_{18}H_{21}BrO_4$, M = 381.26, monoclinic, space group $P2_1/c$, a = 9.1750(10), b = 15.3160(10), c = 11.4560 (10) Å, β = 102.2600(10)°, U = 1573.1(2) Å^3, Z = 4, d_{calc} =1.610 g cm^{-3}, $F(000)$ = 784, μ(MoKα) = 2.632 cm^{-1}, T = 150 K, R_1 = 0.0342, wR_2 = 0.0965, GoF = 1.058, unique data = 4570 (R_{int} = 0.023, KappaCCD diffractometer), 215 refined parameters. CCDC 247812. Crystal data for (±)-**12**: $C_{29}H_{45}NO_4Si_2$, M = 527.84, triclinic, space group $P\bar{1}$, a = 11.2940(10), b = 16.4190(10), c = 17.5230(10) Å, α = 101.6800(10), β = 102.9000(10), γ = 89.8000(10)°, U = 3098.8(4) Å^3, Z = 4, d_{calc} = 1.131 g cm^{-3}, F(000) = 1144, μMoKα) = 0.146 cm^{-1}, T = 150 K, R_1 = 0.0453, wR_2 = 0.1223, GoF = 0.948, unique data = 8593 (R_{int} = 0.0412, KappaCCD diffractometer), 669 refined parameters. CCDC 247814. See http://dx.doi.org/10.1039/b509041e for crystallographic data in CIF or other electronic format.

‖ The structure of (±)-**12** was determined by X-ray analysis, and the stereochemistry of (±)-**13** by NOE experiments (the same effects were observed for (±)-**12** and (±)-**13**).

** The modest yield is due to the fragility of diene (±)-**7**, which decomposes almost as fast as it reacts with **14** (which is less reactive than bromo enone (±)-**8**): 70% of unreacted enone **14** was recovered. In this case, formation of a minor amount of the aromatization product cannot be avoided. Stereochemistry of (±)-**15** was determined by NOE experiments.

†† The stereochemistry of (±)-**16** and (±)-**17** was determined by NOE experiments. Reaction between compounds (±)-**6** and (±)-**8** gave a similar result, showing once again that the bridged structure does not influence the facial selectivity of the dienes.

‡‡ Such as the hydrogen bond postulated by Overman *et al.* for the reaction of (±)-**10** (R = H) with *N*-phenylmaleimide (Scheme 4); in THF, the *anti* : *syn* ratio switches to 64 : 36, and reaches 80 : 20 in methanol.

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