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Unexpected *exo* selectivity for an intramolecular Diels–Alder reaction involving a doubly-activated δ-pentenolide dienophile

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ABSTRACT

The intramolecular Diels–Alder cyclization of a homochiral doubly-activated δ-pentenolide system is described, proceeding predominantly via an *exo* transition state to provide an advanced precursor toward unique stereochemical analogs of (+)-symbioimine.

1. Introduction

The intramolecular Diels–Alder (IMDA) reaction is a powerful tool in organic synthesis, allowing for the controlled formation of two new rings and up to four new stereocenters in a single transformation.[1] Accordingly, the IMDA reaction has played a prominent role in the total synthesis of biologically active natural products.[2] Indeed, the remarkable efficiency of the unimolecular [4 + 2] cycloaddition has inspired several groups to propose IMDA reactions as part of the biosyntheses of a host of diverse polycyclic natural products.[3] For example, Uemura et al. suggested that the biosynthesis of the anti-osteoclastogenic iminium alkaloid (+)-symbioimine **1** could involve either an *exo*-selective IMDA cycloaddition of (*E*)-enone **2**[4a] or an *endo*-selective cyclization of dihydropyridinium **3**[4b] followed by epimerization of the enolizable C-4 stereocenter (Scheme 1). Strong experimental support exists for the latter process,[5] but efforts by both Kobayashi[6] and ourselves[7] suggest that the originally proposed *exo*-selective IMDA cyclization of **2** runs counter to the inherent reactivity of the (*E*,*E*,*E*)-1,7,9-decatrien-3-one framework. For example, the Lewis acid-catalyzed IMDA cyclization of triene (±)-**4a** exclusively provided the *endo* product (±)-**5a** in 88% isolated yield (Table 1).[7] The freely rotating exocyclic C-2 stereogenic center completely dictates the π-facial selectively of the cycloaddition. Attempts to affect a similar *endo* selective Lewis acid-catalyzed IMDA reaction of the corresponding (*Z*)-enone analog of (±)-**4a** once again led to the exclusive formation of *cis*-decalin (±)-**5a**, indicating that enone isomerization occurs significantly faster than cycloaddition. Exchanging the *N*-Boc amine moiety in (±)-**4a** for a silyl ether (+)-**4b** or pivalate ester (+)-**4c** resulted in diminished π-facial selectivity without deterioration of the exclusive *endo* selectivity. The resulting major products, (±)-**5a**, (+)-**5b** and **5c**, are doubly epimeric to (+)-**1** at the C-3 and C-4 stereocenters.

2. Results and discussion

In view of these observations, we sought an alternative toward the *trans*-decalin framework of (+)-**1**.[8] Accordingly, we proposed that the desired stereochemical configuration could be obtained via an *endo*-selective IMDA cyclization of α-acyl-δ-pentenolide **8** (Scheme 2). In order to remain consistent with the precedents of Thomas[9] and Jauch,[10] and in contrast to our previous studies,[7] the term '*endo*' in this circumstance (and throughout the remainder of the paper) refers to the overlap between the diene π-system and the lactone carbonyl (not the ketone carbonyl) in the transition state. Saponification and concomitant decarboxylation of the expectant lactone product **7** would provide the complete carbon framework of (+)-**1** in the correct stereoisomeric configuration. The requisite acyclic triene precursor **8** could be obtained by coupling the known homochiral γ-methyl-δ-pentenolide (−)-**9**[11] and an assortment of carbonyl-based electrophiles, for example, **10** or **11**.[7] Examples involving α-linked-α,β-unsaturated lactones as dienophiles for IMDA reactions are surprisingly sparse.[10] In all previous examples, the participating dienophile is a five-membered γ-butenolide and the major products typically arise from an *endo* transition state.

To date, only a single example exists for an IMDA cyclization involving a doubly-activated α-acyl-α,β-unsaturated lactone dienophile.[12] Specifically, Jauch et al. demonstrated that the α-acyl-γ-butenolide generated by the oxidation of alcohol **12** spontaneously cyclized upon formation at rt to afford a ~5.7:1 ratio of *endo*:*exo* products **13** and **14**, respectively (Scheme 3). With regards to the less reactive six-membered δ-pentenolides, Taguchi and co-workers recently described the Lewis acid-catalyzed *intermolecular* Diels–Alder condensation of (±)-**9** with cyclopentadiene, which afforded a 13:1 *endo*:*exo* ratio.[13] The resulting *endo* product

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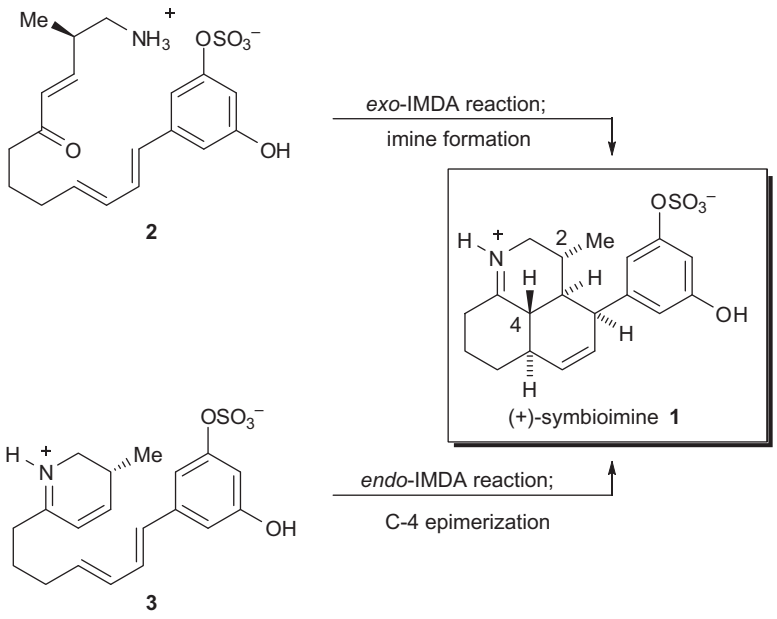
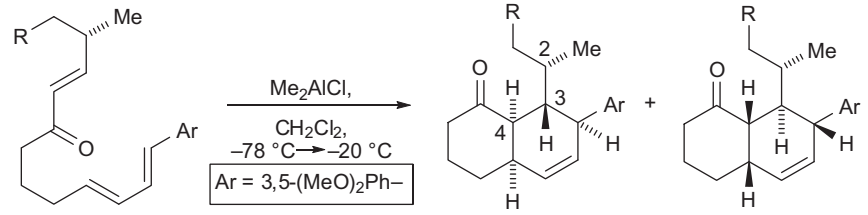


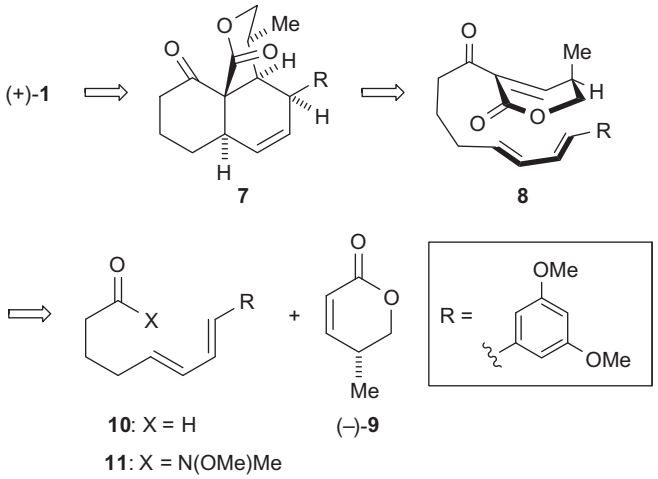
Scheme 1. Uemura's two proposed biosyntheses of (+)-symbioimine.

Table 1
Lewis acid-catalyzed IMDA reaction of (*E*)-enones[7]



Triene	R	Yield[a] (%)	dr (5:6)[b]
(±)-**4a**	NHBoc	88	⩾20:1
(+)-**4b**	$OSiPh_2t$-Bu	76	3:1
(+)-**4c**	OPiv	52	4.5:1

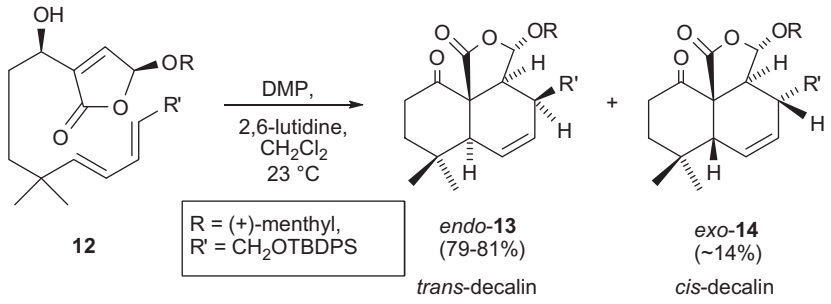
[a] Isolated yield after chromatography.
[b] Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.



Scheme 2. Retrosynthetic analysis of (+)-**1**.

was isolated as a 2.4:1 mixture of π-facial stereoisomers favoring the product arising from the diene approaching opposite the dienophile δ-methyl substituent. Based on these precedents, we felt it reasonable to propose that the IMDA cyclization of triene **8** would favor the desired *endo* product **7**. Accordingly, we set out to rapidly construct the requisite IMDA precursor triene.

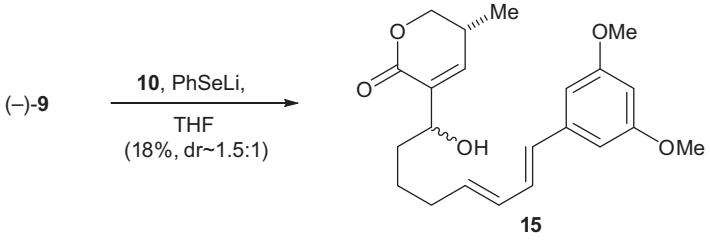
Toward this end, homochiral δ-pentenolide (−)-**9** was readily obtained from ethyl acetate and (+)-(*S*)-Roche ester following an adapted literature protocol.[14] Homochiral lactone (−)-**9** appeared to be an attractive general chiral feedstock in organic synthesis. Examples toward this end are essentially absent in the literature, however.[13,15] While enone (−)-**9** was readily converted into α-bromo, α-iodo, or α-stannane congeners, all of these δ-pentenolides proved remarkably uncooperative as nucleophilic precursors. For example, formation of the corresponding Grignard or vinylzinc species at low temperature following Knochel's protocols[16,17] was feasible, but the resulting organometallic species failed to react even with relatively potent 'soft' electrophiles such as iodine or bis-(4-chlorophenyl)di-sulfide. Various attempts at Pd-catalyzed cross-couplings, either under Stille[18] or Negishi coupling



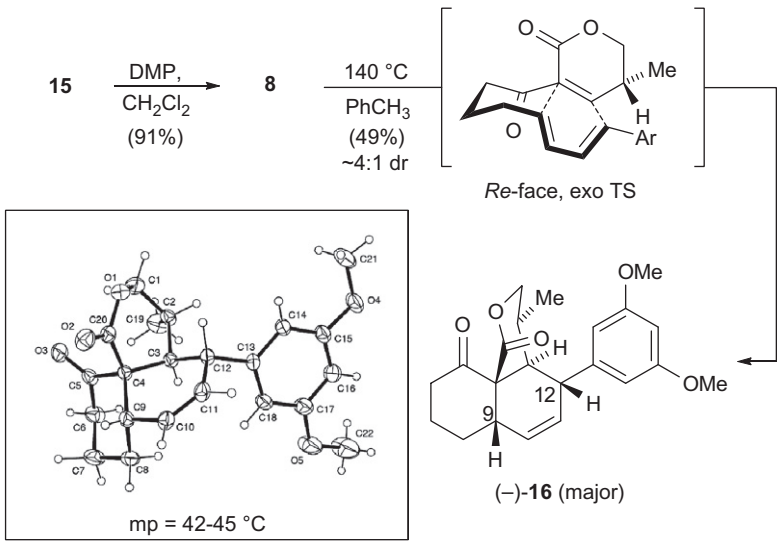
Scheme 3. Jauch's doubly-activated δ-butenolide IMDA reaction.[12]

conditions were unsuccessful. Moreover, in accordance with related reports,[19] the DABCO-mediated Baylis–Hillman condensation of **9** with phenylacetaldehyde did not proceed. The lithium phenylselenide-mediated Baylis–Hillman tactic introduced by Jauch[20] successfully coupled δ-pentenolide (−)-**9** with aldehyde **10**, albeit in low yield (Scheme 4). The unreacted lactone **9** could be recovered from the reaction mixture, but the remaining aldehyde **10** decomposed under the reaction conditions.

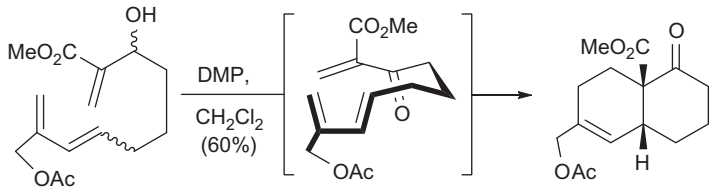
Attempts to initiate an IMDA cyclization of the mixture of epimeric alcohols **15** thermally (140 °C, $PhCH_3$) were not successful.[21] Oxidation to the corresponding ketone **8** was accomplished in high yield using Dess–Martin periodinane (DMP, Scheme 5).[23] Unlike the doubly-activated δ-butenolide **12**,[12] ketone **8** did not spontaneously undergo IMDA cyclization at ambient temperature.[22] Heating the resulting doubly-activated dienophile with toluene in a sealed tube to 140 °C, gave complete conversion to two products in a ~4:1 ratio.[24] Extensive 2D NMR spectroscopic analysis and X-ray crystallography[25] confirmed that the major product was the unexpected *exo* isomer (−)-**16**.[26,27] Resubjection of purified (−)-**16** to the reaction conditions (140 °C, $PhCH_3$, 18 h) resulted in the quantitative recovery of the tricyclic lactone, indicating that the initial product mixture does not represent a thermodynamic equilibrium ratio. The *cis*-decalin (−)-**16** is epimeric to (+)-**1** at C-9 and C-12. Attempts to induce an *intermolecular* Diels–Alder condensation between δ-pentenolide (−)-**9** and diene **11** either thermally (120 °C, $PhCH_3$) or with a Lewis acid (1.5 equiv Me_2AlCl, CH_2Cl_2, −78 °C→−20 °C) in the hopes of procuring the *endo* isomer were not productive.



Scheme 4. Synthesis of triene alcohol **15**.



Scheme 5. Formation and IMDA reaction of α-acyl-δ-pentenolide **8**. Inset: ORTEP diagram (50% probability ellipsoids) for the major IMDA product (−)-**16**, confirming the *exo*-transition state and *Re*-facial selectivity.[25]



Scheme 6. Formation and *exo*-selective IMDA reaction of acrylate **18**.[27]

3. Conclusion

In conclusion while the stereoconfiguration of tricycle (−)-**16** does not match that of (+)-**1**, it does correlate to the absolute stereoconfiguration of the minor IMDA products (−)-**6b** and **6c** obtained in our previous studies.[7] Therefore, constraining the C-2 stereogenic center within the lactone affords a complete reversal of π-facial selectivity without obviating the overlap between the ketone carbonyl and diene in the transition state. Accordingly, we now have two alternative strategies to directly access stereochemical analogs of (+)-symbioimine. We intend to employ these valuable molecular tools to explore the structure–activity relationship of the unique anti-osteoclastogenic alkaloid.

4. Experimental

4.1. (*R*)-5-Methyl-5,6-dihydro-*2H*-pyran-2-one (−)-9

At first, *n*-BuLi (1.6 M in hexanes, 6.2 mL, 9.97 mmol) was added dropwise to distilled diisopropylamine (1.01 g, 9.97 mmol) in THF (10 mL) at −30 °C and let stir 15 min before cooling to −78 °C and adding dry EtOAc (0.97 mL, 9.97 mmol) dropwise. After stirring for 1 h at −78 °C, (2*S*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)-propan-al[14] (1.56 g, 9.05 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred 30 min at −78 °C and then quenched with satd NH_4Cl (20 mL) before extracting with CH_2Cl_2 (2 × 20 mL), drying ($MgSO_4$), and concentrating to a partially solidified oil (1.95 g, 83%). Benzene and *p*-TsOH·H_2O (1.71 g, 8.99 mmol) were then added to the crude product and the mixture was heated at reflux (Dean–Stark) for 7 h. The reaction mixture was diluted with satd $NaHCO_3$ (20 mL) and the resulting organic layer was washed sequentially with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to a black residue before distillation using a Kugelrohr apparatus (1 torr, 90–110 °C) to collect a clear colorless oil (0.78 g, 92%): R_f = 0.27 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (ddd, J = 9.8, 3.5, 0.7 Hz, 1H), 5.93 (dd, J = 9.8, 2.0 Hz, 1H), 4.37 (ddd, J = 11.0, 5.0, 1.1 Hz, 1H), 4.03 (dd, J = 11.0, 8.3 Hz, 1H), 2.72–2.59 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.6, 151.5, 120.0, 72.0, 28.7, 15.3; $[\alpha]_D^{23} = -42.0$ (*c* 1.0, $CHCl_3$); HRMS (ES+) *m/z* 135.0425 [(M+Na)$^+$; calcd for $C_6H_8NaO_2^+$: 135.0417].

4.2. Tricyclic lactone (−)-16

At first, *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.58 mmol) was added dropwise to a solution of diphenyldiselenide (492 mg, 1.58 mmol) in THF (3 mL) at −20 °C. After 20 min, the solution was cooled to −78 °C and a solution of aldehyde **10** (273 mg, 1.05 mmol) and δ-pentenolide (−)-**9** (118 mg, 1.05 mmol) in THF (3 mL) was added. The reaction mixture was kept at −78 °C for 3 h followed by 16 h at −20 °C. The reaction was then quenched with satd NH_4Cl (10 mL), extracted with EtOAc (3 × 10 mL), and dried ($MgSO_4$). The concentrated residue was passed through a silica gel column (50% EtOAc/Hex) to give **15** as a yellow oil and as an inseparable ~1.5:1 mixture of diastereomers (69 mg, 18%). The resulting diastereomeric mixture of alcohols (56 mg, 0.15 mmol) was allowed to stir with Dess–Martin periodinane[23] (96 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) at rt for 4 h. The reaction was diluted with CH_2Cl_2 (3 mL) and washed sequentially with satd $NaHCO_3$ (5 mL), satd $Na_2S_2O_3$ (5 mL), and brine (5 ml) before drying ($MgSO_4$) and concentrating to a yellow oil (50 mg, 91%). A solution of the crude triene **8**[22] (50 mg, 0.13 mmol) in toluene (2 mL, 0.07 M) was heated at 140 °C in a sealed tube for 15 h. ^{1}H NMR analysis of the crude reaction showed two products in a ~4:1 ratio (d, 0.77 and 0.44 ppm). The residue was purified by flash column chromatography (30% EtOAc/Hex) to afford lactone (−)-**16** as an ivory solid (19 mg, 38%): R_f (30% EtOAc/hexanes) = 0.31; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 3H), 5.84 (ddd, J = 9.9, 5.1, 2.5 Hz, 1H), 5.49 (dd, J = 10.0, 1.7 Hz, 1H), 4.41 (dd, J = 12.0, 9.1 Hz, 1H), 3.94 (dd, J = 12.0, 10.5 Hz, 1H), 3.81 (s, 6H), 3.17–3.05 (m, 2H), 2.71 (dt, J = 12.5, 5.5 Hz, 1H), 2.64 (dd, J = 9.4, 1.8 Hz, 1H), 2.53 (ddd, J = 13.2, 5.2, 3.8 Hz, 1H), 2.37–2.28 (m, 1H), 2.18–2.09 (m, 2H,), 1.85–1.67 (m, 2H), 0.78 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.6, 171.8, 161.0, 144.7, 129.0, 128.2, 106.9, 98.0, 69.9, 62.5, 55.3, 48.7, 42.8, 40.9, 39.8, 30.0, 29.9, 26.2, 18.5; IR (cm^{-1}) 3054, 2918, 2848, 1749, 1699, 1595, 1460, 1315, 1265, 1158; $[\alpha]_D^{23} = -119.8$ (*c* 0.40, $CHCl_3$); HRMS (ES+) *m/z* 393.1666 [(M+Na)$^+$; calculated for $C_{22}H_{26}O_5Na^+$: 393.1673]. A crystal suitable for X-ray analysis was obtained by slow evaporation from EtOAc/Hex; mp = 42–45 °C.[25,26]

Acknowledgments

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21. Similarly, the corresponding TBS ethers of **15** did not undergo IMDA reaction with heat (140 °C).
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26. The minor diastereomer could not be isolated in sufficient purity for characterization.
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