EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201200513

A Convergent Hetero-Diels–Alder Strategy for Asymmetric Access to a Lactone Containing Two Lipidic Chains

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Keywords: Lactones / Asymmetric synthesis / Chiral auxiliaries / Cycloaddition / Diastereoselectivity

Eu(fod)$_3$-catalyzed heterocycloaddition of chiral β-alkyl-*N*-vinyl-1,3-oxazolidin-2-ones with a heterodiene bearing a lipidic chain led to heterocycloadducts in high yield with excellent *endo* and facial selectivities. An original lipidic lactone, a potent precursor of a ceramide analog, was obtained in seven steps from the adduct in a convergent manner after appropriate functionalization.

Introduction

Sphingolipids are important membrane constituents of eukaryotic cells that are involved in biological processes such as cell proliferation, differentiation, adhesion, and signal transduction.[1] The study of sphingolipid metabolism and function is an important field of biochemistry. Many research groups have focused their interest on ceramides due to their important role in sphingolipid metabolism.[2] Ceramides are potent lipid mediators of many cellular functions including proliferation, differentiation, and apoptosis.[3] For example, induction of apoptotic cell death has been observed with two aromatic ceramide analogs, MAPP (**1**)[4] and B13 (**2**, Figure 1).[5] As part of an ongoing program devoted to the synthesis of galactosylceramide analogs,[6] we focused our attention on conformationally rigid galactosylceramide (Figure 2). Some constrained ceramide analogs such as **3** and **4** have already been described and have shown potent biological activities.[2] During the time of this study, Vasella et al. reported an efficient synthesis of constrained ceramide analogs **5** (Figure 1) that showed biological activities as inhibitors of sphingosine kinase or as *i*NKT cells ligands.[7] Compound **5a** (R = H) inhibited SPHK1 with an IC_{50} of 9.8 μM. Interestingly, only compounds **5** containing the two alkyl chains (R and R′) in a *trans* relationship proved to activate *i*NKT cells (Figure 1). We describe herein the synthesis of lactone **7**, which is a potential precursor to access ceramide analogs **6**, and the corresponding constrained galactosylceramide (Figure 2).[8]

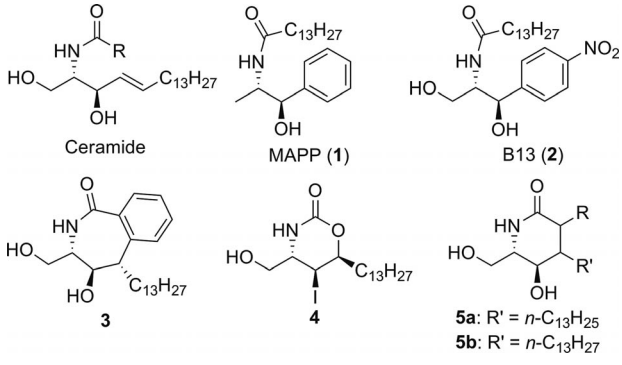

Figure 1. Structures of some ceramide analogs.

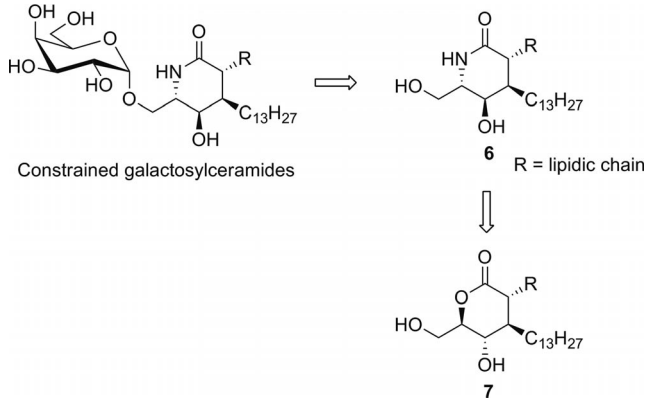

Figure 2. General strategy to access targeted constrained ceramides and their corresponding constrained galactosylceramides.

Results and Discussion

The key step of our synthetic strategy involved an asymmetric inverse-electron-demand (IED) heterocycloaddition

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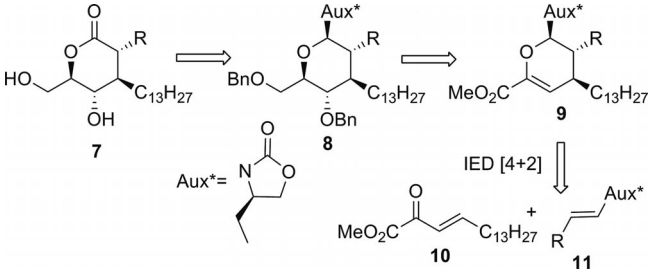
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200513.

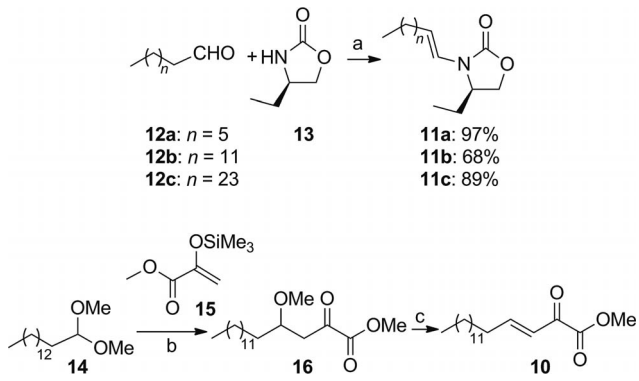
between heterodiene **10** and dienophile **11** (Scheme 1). Contrary to the normal-electron-demand [4+2] pathway, the IED [4+2] one displays optimal convergence, as it involves two cycloreactants each incorporating a lipidic chain. To the best of our knowledge, the formation of dihydropyranes by [4+2] cycloaddition of oxadiene has never been extended to cycloreactants bearing two lipidic chains. Dujardin et al. reported that (4*R*)-4-ethyl-3-vinyl-1,3-oxazolidin-2-one[9] was an efficient dienophile partner in Eu(fod)$_3$-catalyzed asymmetric [4+2] cycloaddition with β,γ-unsaturated α-keto esters, leading to heterocycloadducts with high *endo* and facial selectivities.[10] Furthermore, it has been shown that the use of chiral β-substituted *N*-vinyl-1,3-oxazolidin-2-ones afforded heterocycloadducts with three controlled contiguous stereogenic centers with a similar level of diastereocontrol.[11] Although valuable methods involving asymmetric catalyzed Diels–Alder reactions have been developed in the last decade, their efficiency towards the particular case of an (*E*)-β-substituted dienophile has not yet fully demonstrated.[12]



Scheme 1. Retrosynthetic strategy.

To the best of our knowledge, the synthesis of heterodiene **10** and *N*-vinyl-1,3-oxazolidin-2-ones of type **11** and their use in [4+2] cycloaddition have not been described to date. We first explored the synthesis of β-alkyl-*N*-vinyl-1,3-oxazolidin-2-ones **11a**–**c** and their reactivity towards β,γ-unsaturated α-keto ester **10** under Lewis acid conditions. β-Alkyl-*N*-vinyl-1,3-oxazolidin-2-ones **11a**–**c** were conveniently prepared in a straightforward manner by a one-step reaction of the corresponding aldehydes **12a**–**c** with (*R*)-5-ethyl-1,3-oxazolidin-2-one (**13**) under acidic conditions.[13] (*E*)-Isomer dienophiles **11a**–**c** were then isolated in good to high yields (68–97%, Scheme 2). Heterodiene **10** was prepared in two steps from acetal **14**. Reaction between acetal **14** and freshly prepared methyl pyruvate derived silyl enol ether **15** furnished compound **16** in 95% yield. Heating of **16** in the presence of silica in toluene at 110 °C afforded (*E*)-isomer γ-tridecanyl-β,γ-unsaturated α-keto ester **10**[14] in 94% yield (Scheme 2). It is noteworthy that a prolonged heating time led to unidentified degradation products.

Having both partners in hand, we then investigated the key heterocycloaddition between chiral β-substituted *N*-vinyl-1,3-oxazolidin-2-one **11a** and γ-tridecanyl-β,γ-unsaturated α-keto ester **10** by using Eu(fod)$_3$ as a catalyst or $SnCl_4$ as a promoter. With Eu(fod)$_3$ in cyclohexane at 80 °C, the corresponding cycloadduct was isolated in 51% yield when using only 1 equiv. of the heterodiene. With



Scheme 2. Preparation of heterodiene **10** and dienophiles **11**. Reagents and conditions: (a) CSA, toluene, 110 °C. (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 95%. (c) Silica, toluene, 110 °C, 99%.

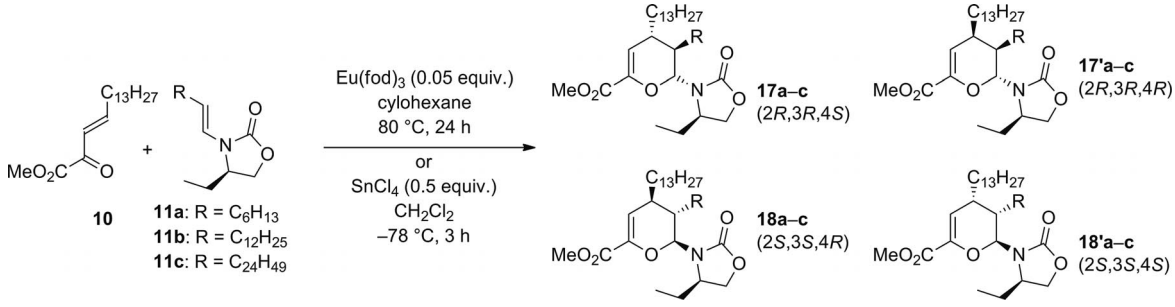
1.5 equiv. of the heterodiene, the yield of the reaction reached 91%. This difference in yield is due to the partial decomposition of the heterodiene under the reaction conditions. In both cases, the reaction proceeded with high *endo* and facial selectivities (Table 1, Entry 1). The *endo* control was fully established by analysis of the NMR spectroscopic data. Only trace amounts of the *exo* cycloadducts derived from dienophile **11a** were detected in the ^{1}H NMR spectrum of the crude product. It is noteworthy that the same range of selectivities and high yields were observed on larger scale (up to 40 mmol, Table 1). Under the same conditions, dienophiles **11b** and **11c** also provided excellent results in terms of yields and selectivities (Table 1, Entries 2 and 3).

When the reaction between dienophiles **11a**–**c** and heterodiene **10** was performed with $SnCl_4$, a reverse facial selectivity was observed that agreed with a previous report.[11a,11b] However, yields remained significantly low (40–46%) due to poor solubility of one or both lipidic partners in dichloromethane at low temperature (Table 1, Entries 4–6). Neither the dilution of the reaction mixture by addition of dichloromethane or a less polar solvent (heptane), nor the replacement of dichloromethane by toluene, were able to improve significantly the yield of the heterocycloaddition.

Both cycloadducts **17a** and **18a** displayed a NOESY correlation between H^c and H^d confirming an *endo* approach during the cycloaddition. Furthermore, only diastereoisomer **17a** displayed a NOESY correlation between H^a and H^b confirming the absolute configuration of the cycloadduct in accordance with the previously observed selectivity[11a] (Figure 3). The oxazolidinone moiety adopts a conformation that places the carbonyl group orthogonal to the average plane of the dihydropyran ring.[15] The ethyl group of the oxazolidinone moiety is thus located in the less bulky position, that is, below the molecule placing H^a in a position close to H^b.

Further functionalization of cycloadduct **17a** was performed to obtain lactone **7**. Reduction by using a DIBAL-H solution in the presence of $BF_3{\cdot}OEt_2$ furnished allylic alcohol **19** (Scheme 3). The addition of $BF_3{\cdot}OEt_2$ to the

Table 1. Heterocycloaddition reaction between **10** and **11a–c**.



Entry	11	Lewis acid	Yield[a] [%]	17+18/17′+18′	17/18[b]
1[c]	**11a**	$Eu(fod)_3$[d]	91	97:3[d]	96:4
2	**11b**	$Eu(fod)_3$[d]	92	96:4[d]	95:5
3	**11c**	$Eu(fod)_3$[d]	94	95:5[d]	98:2
4	**11a**	$SnCl_4$	46	85:15	5:95
5	**11b**	$SnCl_4$	45	86:14	2:98
6	**11c**	$SnCl_4$	40	75:25	3:97

[a] Isolated yield after purification. [b] Determined from the ^{1}H NMR spectrum of the crude product. [c] Scale of 40 mmol: **17/18** = 93:7. [d] This ratio refers to *endo*/*exo* ratio (concerted mechanism).

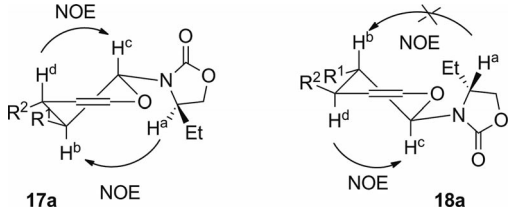
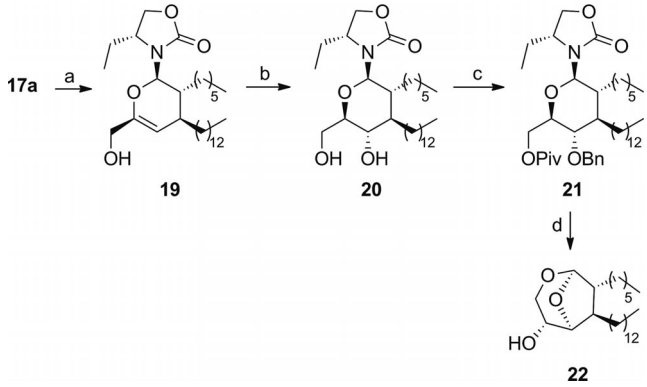


Figure 3. NOESY correlation observed with **17a** and **18a**.

reaction mixture is crucial to avoid the concomitant reduction of the oxazolidinone function.[16] The hydroboration/oxidation sequence by using trimethylamine *N*-oxide (TAO) as the oxidant[17] was then performed on the allylic alcohol to furnish diol **20** in 81% over two steps (Scheme 3). Only one diastereoisomer was detected by ^{1}H NMR spectroscopy, and the overall *trans* relationship between all vicinal protons of the THP ring was assigned subsequently from the ^{1}H NMR spectroscopic data of derivative **21**.



Scheme 3. Synthesis of bicyclic compound **22**. Reagents and conditions: (a) DIBAL-H, BF_3·OEt_2, CH_2Cl_2, –78 °C, 90%. (b) BH_3·Me_2S, THF, r.t. then TAO, THF, 65 °C, 91%. (c) 1. PivCl, pyr., CH_2Cl_2, r.t.; 2. NaH, TBAI, BnBr, THF/DMF, r.t., 77%. (d) Silica, H_2SO_4 (aq.), CH_2Cl_2, 40 °C, 35%.

The next challenging step was the removal of the chiral auxiliary, 1,3-oxazolidin-2-one, as only few examples have been reported.[18] Classical orthogonal protection was first performed leading to **21** in 77% yield (Scheme 3). The formation of the corresponding lactol was first envisaged by carrying out the reaction of compound **21** in a 20% aqueous sulfuric acid solution in the presence of silica. However, bicyclic compound **22** was isolated in 35% yield along with remaining compound **21**.

The structure of acetal **22** was assessed on the basis of 2D NMR spectroscopic data (Figure 4). The NMR signals of the acetal proton and carbon could be unambiguously identified from their chemical shifts. This assignment was confirmed by an HMBC experiment, which showed a correlation of acetal proton H^a with the carbon atoms of the CH_2O group and the ring junction carbon atom (C^f and C^d). Then, the corresponding proton was clearly identified and positioned in the molecule on the basis of COSY and HSQC results.

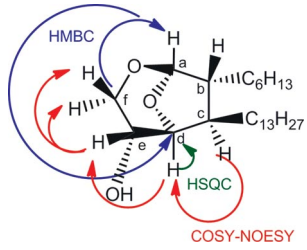
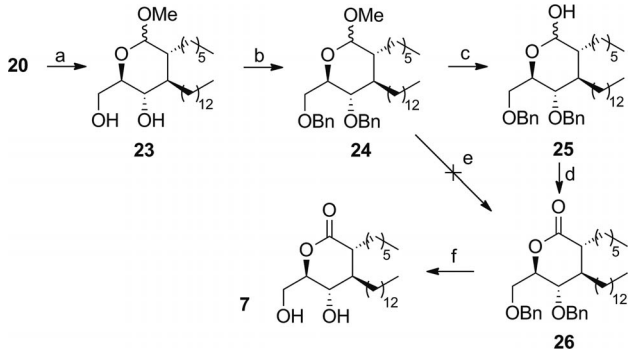


Figure 4. 2D NMR spectroscopic data of bicyclic compound **22**.

The chiral auxiliary of diol **20** was then removed under mild conditions (acetyl chloride in methanol at 65 °C) to furnish compound **23** as a mixture of anomers in 68% yield. Diol **23** was then protected with benzyl groups under usual conditions. However, the direct obtention of lactone **26** by oxidation of resulting protected acetal **24** under Grieco's conditions[19] failed. Finally, treatment of compound **24**

with an aqueous sulfuric acid solution led to **25** as a mixture of the two desired anomeric lactols in 76% yield, which was converted into lactone **26** by oxidation with TPAP and NMO in dichloromethane in the presence of molecular sieves (76% yield). Hydrogenolysis of **26** over palladium hydroxide on charcoal led to targeted lactone **7** in 41% yields (Scheme 4).



Scheme 4. Access to lactone **7**. Reagents and conditions: (a) AcCl, MeOH, r.t. to 65 °C, 68%. (b) NaH, TBAI, BnBr, DMF, r.t., 92%. (c) H_2SO_4 (aq.), acetone, 85 °C, 76%. (d) TPAP, NMO, 4 Å MS, CH_2Cl_2, r.t., 76%. (e) *m*-CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, r.t. (f) H_2, 20% $Pd(OH)_2/C$, MeOH, r.t., 41%.

Conclusions

In conclusion, we have successfully performed a hetero-Diels–Alder reaction between a β-alkyl-*N*-vinyl-1,3-oxazolidin-2-one and a heterodiene each containing a lipidic chain. When $Eu(fod)_3$ was used as the catalyst, the heterocycloaddition occurred with high yield and diastereoselectivities independently of the nature of the dienophile. The Lewis acid catalyzed conditions used [$Eu(fod)_3$ in refluxing cyclohexane] were fully suitable with the lipophilic nature of the two substrates, permitting the reaction to take place in homogeneous medium. Moreover, the use of $SnCl_4$ allows for practical facial stereodivergence. The whole process takes advantage of the availability of enamide **11** as a dienophile.[20] After appropriate transformations of cycloadduct **17a**, efficient conditions for removal of the chiral auxiliary were developed to allow access to key lactone **7** featuring the two lipidic chains in a *trans* relationship. Further studies on the synthesis of conformationally rigid ceramide analogs and galactosylceramides are currently underway.

Experimental Section

Typical Procedure for Cycloaddition with [$Eu(fod)_3$]: A solution of dienophile **11** (1 equiv.), heterodiene **10** (1.5 equiv.), and $Eu(fod)_3$ (0.05 equiv.) in cyclohexane (1 mL/mmol) was heated under reflux for 1 d. After cooling to room temperature, the solvent was removed, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1→95:5).

Typical Procedure for Cycloaddition with $SnCl_4$: To a solution of dienophile **11** (1 equiv.) and heterodiene **10** (2 equiv.) in dry dichloromethane (7 mL/mmol) at –78 °C was added a solution of $SnCl_4$ in dichloromethane (1.0 M, 0.5 equiv.). The solution was stirred at –78 °C for 3 h, quenched with a saturated aqueous $NaHCO_3$ solution (5 mL), and then warmed up to room temperature. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1→95:5).

Typical Procedure for the Removal of the Oxazolidinone: To a solution of diol **20** (511 mg, 1.00 mmol) in dry methanol (10 mL) at 0 °C was added dropwise acetyl chloride (5 mL). The solution was stirred at 0 °C for 0.5 h, at room temperature for 2 h, and then under reflux for 2 h. After cooling to room temperature, a saturated aqueous $NaHCO_3$ solution (15 mL) was added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3× 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 95:5→90:10) to lead to acetal **23** as a mixture of anomers (291 mg, 0.680 mmol, 68%) as a white solid.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

The authors thank the Centre National de la Recherche Scientifique (CNRS), the Ministère de l'Enseignement Supérieur et de la Recherche, and the Region Pays de la Loire for their financial support. We also thank the Agence Nationale de la Recherche (ANR-08-PCVI-0024, Galcerdeo) for financial support. Acknowledgments are also made to F. Legros, P. Gangnery, and A. Durand for their technical assistance.

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[14] The configuration of the double bonds for compounds **10** and **11** is (*E*) and their coupling constants are in accordance with the values already described in the literature: For type-**11** enamides a coupling constant of 14.5 Hz for the (*E*) geometry is generally observed (see Z. Song, T. Lu, R. Hsung, Z. Al-Rashid, C. Ko, Y. Tang, *Angew. Chem. Int. Ed.* **2007**, *46*, 4069) instead of 8.5 Hz for the (*Z*) configuration (see X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, M. R. Tracey, *J. Org. Chem.* **2006**, *71*, 4170–4177). For heterodiene **10**, we observed a coupling constant of 15.9 Hz, which is similar to those found by Alexakis (L. Gremaud, A. Alexakis, *Angew. Chem. Int. Ed.* **2012**, *51*, 794–797), by Lassaletta (R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, 3303–3306), or by Paulmier (S. Boivin, F. Outurquin, C. Paulmier, *Tetrahedron* **1997**, *53*, 16767–16782) for such (*E*)-β,γ-insaturated α-oxo-esters.
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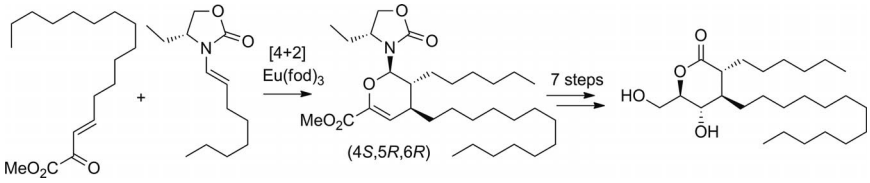
[20] Independent of the stereochemistry, practical access to enamide **11** compares well with that of the corresponding vinyl ether derivative.

Received: April 19, 2012
Published Online: ■

Cycloaddition



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