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Total syntheses of (±)-*cis*- and (±)-*trans*-neocnidilides

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ABSTRACT

Total syntheses of two antimicrobial natural products (±)-*cis*-neocnidilide and (±)-*trans*-neocnidilide starting from a readily preparable cyclohexa[*b*]-fused 5-oxabicyclo[2.1.1]hexane derivative are presented. The diastereomeric tetrahydrofuran tricarboxylate epimers obtained from a $BF_3{\cdot}OEt_2$ promoted Grob-type fragmentation of the oxa-bicycle derivative were converted into title natural products by employing pyridinium dichromate/acetic anhydride mediated bis-oxidative cleavage reaction.

Phthalides are the components of taxonomic groups of the plant family Apiaceae.[1] The stereo isomers *cis*- and *trans*-neocnidilides (**1** and **2**) are the tetrahydro derivatives of phthalides. The compounds **1** and **2** are present in *Apium graveolens* L. including their structural analogues. Isolation and structure confirmation of **2** were reported by Mitauhashi et al. in 1964.[2] Later, Fischer et al.[3] have isolated and reported *cis*-neocnidilide (**1**) from *A. graveolens* L., and spectroscopic data comparison with previously isolated phthalides showed that the structure is similar to previously reported isocnidilide. Some naturally occurring 3-butyltetrahydrophthalides are represented in Figure 1. Literature survey for biological features of these natural products revealed that the compound **2** inhibits the growth and toxin production of mycotoxin-producing fungi.[4] As additional factors for biological activity profile of **2**, (−)-*trans*-neocnidilide and its racemic mixture showed inhibiting activity against microorganisms *Aspergillus niger*, *Cochliobolus miyabeanus*, and *Pyricularia oryzae* at the range of 50 μg/disk to 300 μg/disk concentration.[4] In continuation of hunt for new bioactive compounds in natural resources, Nair and co-worker[5a] isolated **2** from *A. graveolens* along with two other hydroxyl tetrahydrophthalides, and biological assay for **2** displayed noteworthy mosquitocidal, nematicidal, and antifungal activities compared to other two additionally isolated phthalides, which are having conjugation to lactone carbonyl at the ring junction. Moreover, during last decade, Miyazawa and co-workers[5b] have isolated *trans*-neocnidilide (**2**) from *Cynoglossum officinale* including three other butyl phthalides.

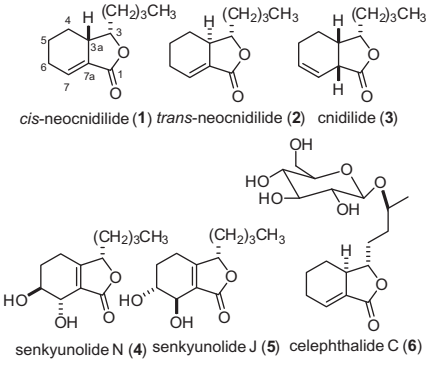

Figure 1. Some naturally occurring 3-butyltetrahydrophthalides.

The larvicidal activity test for **2** against *Drosophila melanogaster* shows LC_{50} value 9.90 μmol/mL, and structure–activity relationship confirms that the presence of conjugation with lactone carbonyl moiety plays a crucial role for larvicidal activity. Also, the acute adulticidal activity test report for **2** shows 97% mortality at a concentration of 50.0 μg/adult with LD_{50} value 10.82 μg/adult. Notably, the difficulty in isolation of pure **1** is the demerit for evaluating more biological activity for *cis*-neocnidilide.[3]

The literature survey revealed that very few synthetic routes have been reported for the synthesis of structurally simple 3-butyltetrahydrophthalides **1** and **2**.[6] In the synthesis of (−)-*cis*-neocnidilide reported by Tanaka et al.,[7] it has been demonstrated that, the

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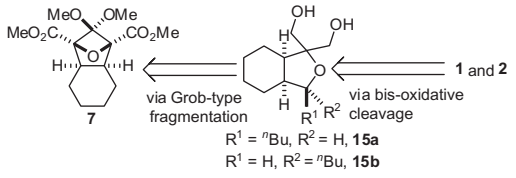
severe steric hindrance between the butyl chain and the olefinic proton in the most preferable *exo* transition state of intra molecular Diels–Alder reaction of triene ester would diminish the formation of **3**–**3a** *cis* adduct. Eventually, the variance in position of butyl chain of triene ester afforded 1:1.4 ratio of **3**–**3a** *cis* and **3**–**3a** *trans* adduct, and then minor isomer was utilized to accomplish the synthesis of **1** via reduction of non-conjugated double bond and recreation of conjugated unsaturation to lactone. Moreover, McClure strategy[8] for the total synthesis of both **1** and **2** from dihydrofuran involves utilization of phosphonates, which are obtained via their previously reported condensation reaction involving pentacovalent oxaphosphoranes and carbonyl compounds. However, this synthesis requires construction of cyclohexene fused lactone system and late stage Barton deoxygenation was employed to complete the total synthesis of **1** and **2**. Therefore, we sought an alternative strategy for the synthesis of both natural products.

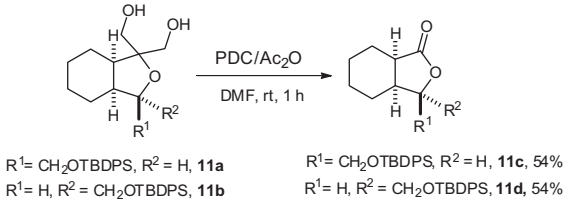
Grob-fragmentations[9] and ring cleavage reactions are generally efficient, these have been utilized as key reactions in numerous natural products' synthesis and construction of organic frame works.[10,11] Recently, we have reported[12] a $BF_3{\cdot}OEt_2$-mediated Grob-type fragmentation reaction of compound **7**. It provides tetrahydrofuran tricarboxylates **8a**,**b** (ratio **8a**:**8b** = 3:1) in near quantitative yield. The cyclohexa[*b*]-fused 5-oxabicyclo[2.1.1]hexane **7** could be prepared in gram-scale quantities from commercial available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene and cyclohexene (three steps, overall yield 80%).[13,14] The ready availability of **7** inspired us to utilize it for the synthesis of **1** and **2** employing Grob-type fragmentation[12] and bis-oxidative cleavage reactions as key steps as represented in Scheme 1.[15–17]

Octahydroisobenzofuran methanols **10a** and **10b** were prepared starting from chromatographically well separable THF derivatives **8a** and **8b**, respectively. The transformation of **8a**–**10a** is depicted in Scheme 3, it involves conversion of THF tricarboxylate **8a** to corresponding triol **9a** by reduction with $LiAlH_4$ in refluxing THF (74% yield). When the compound **9a** was subjected for acetonide protection, it afforded the required THF alcohol **10a** along with a less polar mixed acetal (confirmed by ^{1}H NMR),[16] which was selectively deprotected by treatment with pyridinium *p*-toluenesulfonate in MeOH at 0 °C for 50 min to afford alcohol **10a** with an overall yield of 90% (from two steps). At this stage, we turned our attention to demonstrate the feasibility of our proposed pathway for the synthesis of **1** and **2** via bis-oxidative cleavage reaction. The alcohol **10a** was protected as TBDPS ether and subsequent acetonide deprotection with PPTS (10 mol %) in MeOH at 50 °C afforded dimethanol THF **11a** with 84% yield (from two steps) as depicted in Scheme 3. The similar experimental procedures were adopted for preparation of **11b** from **8b** as detailed in Scheme 4. Then, exposure of THFs **11a** and **11b** to bis-oxidative cleavage with PDC/Ac_2O gave lactones **11c** and **11d**, respectively, in moderate yields (54%) as represented in Scheme 2.

After demonstrating the bis-oxidative cleavage reaction for THF alcohols **11a** and **11b**, we committed to achieve the synthesis of **1** and **2**, then our attention was drawn to convert the free hydroxymethyl group of **10a** to ^{n}butyl chain. Initially, our effort for direct conversion[18] of alcohol **10a** to alkyl chain by converting it into triflate and treatment with ^{n}propyl magnesium bromide failed to



Scheme 1. Retrosynthetic analysis of **1** and **2** from **7**.



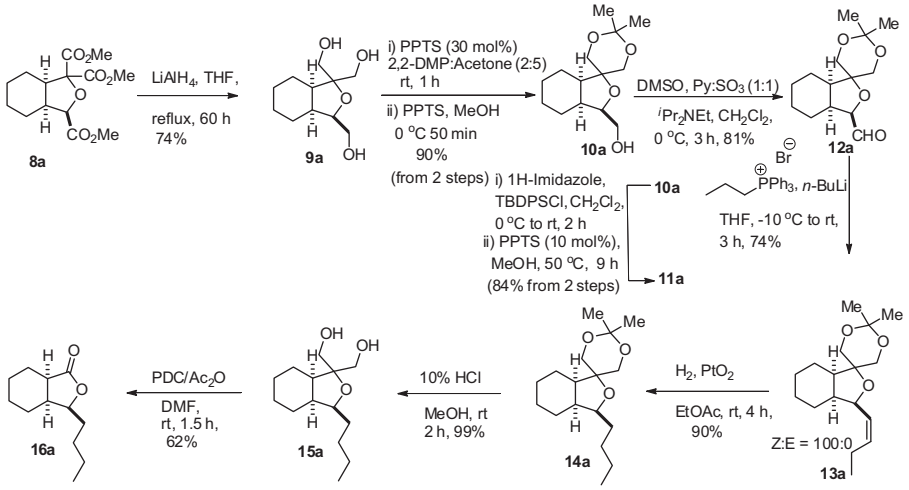
Scheme 2. Demonstration of bis-oxidative cleavage for THF diols **11a** and **11b**.

afford the required product. To overcome this difficulty, we converted alcohol **10a** to corresponding aldehyde by Parikh–Doering oxidation employing Hünig's base (^{i}Pr$_2$NEt)[19] which afforded aldehyde **12a** in 81% yield without any epimerization despite being sterically congested. Then, aldehyde **12a** was subjected to Wittig olefination using triphenyl(propyl)phosphonium bromide and *n*-BuLi to obtain olefin **13a** (*Z*/*E* = 100:0) in 74% yield.[20] Further, the hydrogenation of olefin **13a** using H_2, Pd-C gave complex mixture due to double bond isomerization.[21] Afterward, exposure of **13a** to hydrogenation using Adam's catalyst (PtO_2)[22] delivered compound **14a** in 90% yield, with little amount of olefin isomerized product (confirmed by ^{1}H NMR). The acetonide deprotection of **14a** with 10% HCl in MeOH afforded **15a** in 99% yield which upon bis-oxidative cleavage delivered **16a** in 62% yield (Scheme 3).

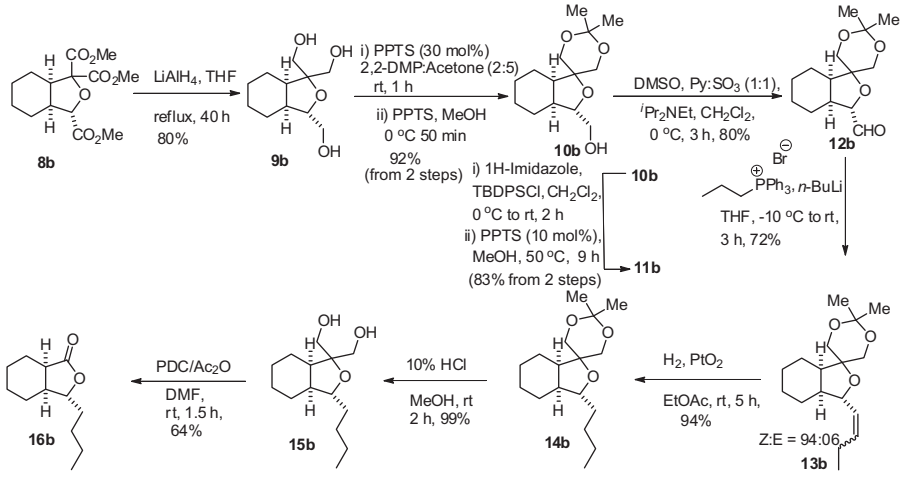
On the other hand, having sufficient amount of minor octahydroisobenzofuran derivative **8b**, we proceeded to synthesize lactone **16b** similar to **16a** as depicted in Scheme 4. In this part, the triol **9b** was obtained in 80% yield (40 h) followed by mono alcohol **10b** after acetonide protection. Then, alcohol **10b** was oxidized to corresponding aldehyde **12b** with 80% yield under similar oxidation condition as **12a**. Further, when Wittig olefination was carried out for the compound **12b**, *Z*/*E* mixture of olefin **13b** resulted in 94:06 ratio with 72% yield. Then, on treatment of *Z* and *E* mixture of alkene **13b** with H_2/cat. PtO_2, no isomerized product was observed and delivered the compound **14b** in 94% yield. The diol **15b** obtained after removal of the acetonide group of **14b** was subjected to bis-oxidative cleavage with PDC/Ac_2O to afford lactone **16b** in 64% yield.

After successfully synthesizing lactones **16a** and **16b**, we focused our attention for creating the conjugated unsaturation in a regioselective manner via α-bromination and elimination sequence. From the literature,[23] we believe that bromination of lactone could be accomplished directly in the presence of LDA without converting lactone into acid sensitive silyl ketene.[7] Then, the exposure of compounds **16a** and **16b** to molecular bromine in the presence of LDA in THF at −78 °C yielded diastereomerically pure α-bromo lactones **17a** and **17b**, respectively, in moderate yields along with substantial recovery of starting materials as depicted in Scheme 5. When we subjected compound **17a** for dehydrobromination with DBU in refluxing toluene, incomplete consumption of starting material was observed. Then treatment of **17a** with DBU (3.0 equiv) in xylene at 140 °C afforded (±)-*cis*-neocnidilide (**1**) and **18a**[24] in ratio 9:1. Due to isomerization of conjugated double bond of **1**, trace amount of (±)-cnidilide **3** (confirmed by ^{1}H NMR and IR spectra) was also observed. On the other hand, elimination of **17b** with DBU (2.0 equiv) in toluene yielded (±)-*trans*-neocnidilide (**2**) and **18a** with 72% yield (**2**:**18a** = 17:03). Both ^{1}H and ^{13}C NMR data of synthesized natural products **1** and **2** are having close agreement with literature reported data (for detail see S57 and S58 in Supporting information).[25]

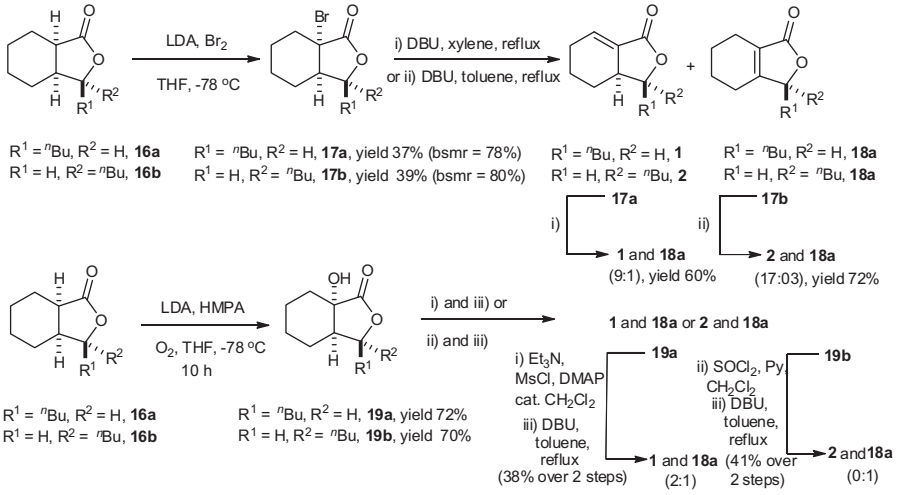
In an effort to enhance the overall yields, we turned our attention to synthesize α-hydroxy lactones **19a** and **19b**. Our results on the synthesis of **1** and **2** via α-hydroxylation and elimination route from lactones **16a** and **16b** are depicted in Scheme 5. The treatment of **16a** and **16b** with molecular oxygen using LDA/HMPA in



Scheme 3. Synthesis of lactone **16a** from **8a**.



Scheme 4. Synthesis of lactone **16b** from **8b**.



Scheme 5. Completion of total synthesis of (±)-*cis*-neocnidilide (**1**) and (±)-*trans*-neocnidilide (**2**) from **16a** and **16b**, respectively.

THF afforded **19a** and **19b** in 72% and 70% yields, respectively.[26] Further, alcohol **19a** was converted into methanesulfonate, and the mesylate was subjected to elimination with DBU in refluxing toluene to afford **1** and **18a** in 2:1 ratio in 38% yield (over two steps). In view of the fact that, elimination of mesylate derivative of alcohol **19a** gave moderate regioselectivity and lower yield, we

further attempted dehydration of alcohol **19b**, intended to enhance the selectivity in formation of unsaturation. Compound **19b** was treated with $SOCl_2$ and pyridine in CH_2Cl_2 and the resulting product was then reacted with DBU (2.0 equiv) in refluxing toluene (2 h). This afforded **18a** with complete reversal in regioselectivity (**2**:**18a** = 0:1).

In conclusion, we have accomplished the total synthesis of (±)-*cis*-neocnidilide and (±)-*trans*-neocnidilide from an oxa-bridged compound **7** using C-C sigma bond cleavage reactions. The chromatographically well separable THFs **8a** and **8b** were utilized independently for the synthesis of **1** and **2**. The synthesis has been achieved with key reactions involving transformation of aldehyde to alkyl chain using Wittig olefination followed by hydrogenation and pyridinium dichromate/acetic anhydride mediated bis-oxidative cleavage. Additionally, regioselective creation of conjugated double bond was demonstrated both via α-bromo and α-hydroxy lactones.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectroscopic data, copies of ^1H, ^{13}C spectra for all reported compounds and DEPT 135, APT spectra for selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.007.

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25. (±)-*cis*-Neocnidilide (**1**): R_f = 0.3 (5% EtOAc in hexane, silica gel TLC), colorless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (q, 1H, *J* = 3.3 Hz), 4.65 (td, 1H, *J* = 8.9, 3.2 Hz), 3.02–3.09 (m, 1H), 2.30–2.37 (m, 1H), 2.14–2.26 (m, 1H), 1.87–1.98 (m, 2H), 1.42–1.60 (m, 2H), 1.25–1.39 (m, 6H), 0.90 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 136.2, 129.6, 81.8, 39.7, 31.5, 27.5, 25.1, 22.6, 22.5, 21.2, 13.9; IR ν_{max} (neat): 2927, 2856, 1757, 1683, 1454, 1224, 1184, 1093, 1027 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}NaO_2$ $[M+Na]^+$ 217.1204, found 217.1191.
(±)-*trans*-Neocnidilide (**2**): R_f = 0.3 (5% EtOAc in hexane, silica gel TLC), colorless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (q, 1H, *J* = 3.4 Hz), 3.97 (ddd, 1H, *J* = 8.8, 7.6, 5.1 Hz), 2.45–2.54 (m, 1H), 2.30–2.39 (m, 1H), 2.13–2.24 (m, 1H), 2.03–2.09 (m, 1H), 1.91–1.96 (m, 1H), 1.70–1.81 (m, 2H), 1.47–1.55 (m, 2H), 1.32–1.45 (m, 3H), 1.12–1.25 (m, 1H), 0.92 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 135.2, 131.1, 85.3, 43.1, 34.3, 27.5, 25.4, 25.0, 22.5, 20.7, 13.9; IR ν_{max} (neat): 2929, 2859, 1758, 1682, 1455, 1326, 1248, 1224, 1182, 1085 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}NaO_2$ $[M+Na]^+$ 217.1204, found 217.1192.
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