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Sequential transhalogenation and Heck reaction for efficient access to dioxo-tetrasubstituted 2,4 *E*,*E*-dienes: synthesis of segment C1–C6 of apoptolidin

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Abstract—Efficient access to dioxo-tetrasubstituted 2,4 ***E***,***E***-dienes is developed in three steps from commercially available starting materials via sequential transhalogenation and Heck reaction, which provides potentially useful synthons for the synthesis of a tetrasubstituted conjugated diene structure in complex molecules. Thereby, segment C1–C6 of apoptolidin is synthesized.

Potential anticancer agents, apoptolidin (**1**)[1] and FD-891 (**2**)[2] as well as apoptosis inducer mycolactone B (**3**)[3] all have a common tetrasubstituted conjugated ***E***,***E***-diene structure (Fig. 1), which can be envisioned as derived from dioxo-tetrasubstituted 2,4 ***E***,***E***-dienes. The impressive biological activities and structural novelty as well as complexity have promoted a number of synthetic studies towards total syntheses of these naturally occurring products, and synthetic strategies associated with these complex molecules, especially for

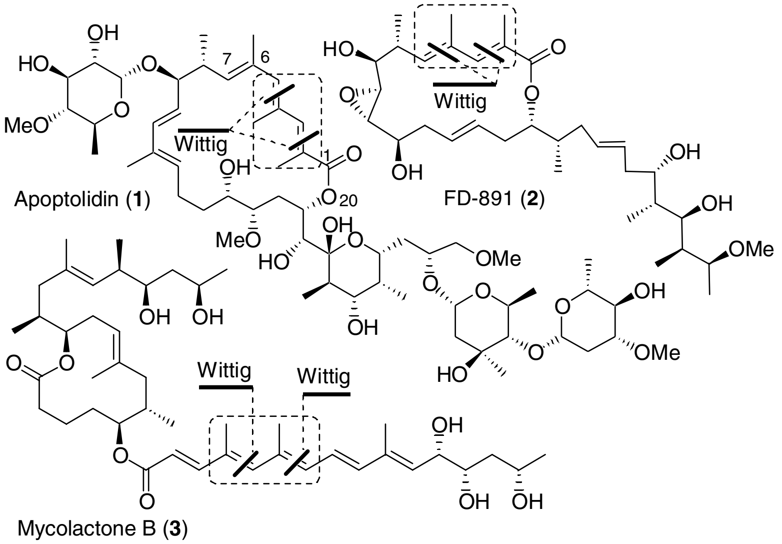

Figure 1.

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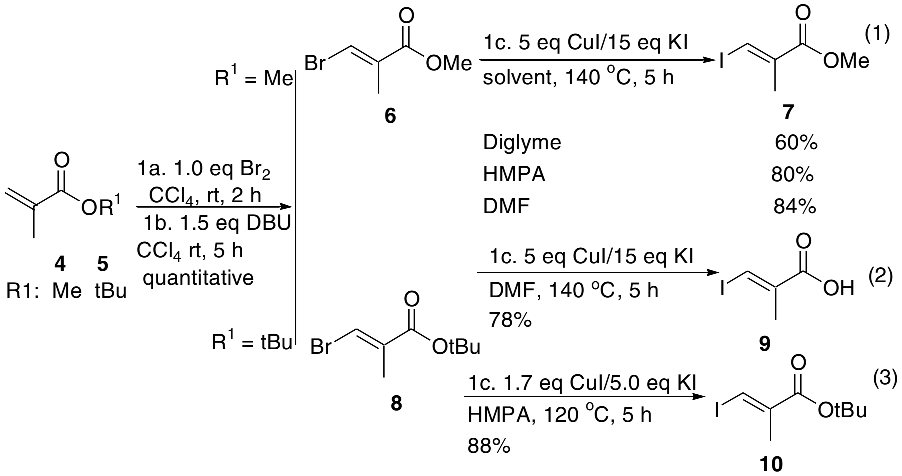
constructing the diene structure, continue to be of great interest.[4–7]

Aside from one of Nicolaou's approaches to the tetrasubstituted diene in the total synthesis of **1**,[4] other constructions of the diene structure of **1**,[4,5] **2**[6] and **3**[7] all feature double Wittig-type homologations (Fig. 1). Herein, we report a new approach to the diene structure by developing efficient access to dioxo-tetrasubstituted 2,4 ***E***,***E***-dienes (Table 1, **13**–**16**) as synthons. The dioxo-tetrasubstituted 2,4 ***E***,***E***-dienes are synthesized in three steps from commercially available starting materials via sequential transhalogenation and Heck reaction, and the synthesis of segment C1–C6 of apoptolidin is illustrated.

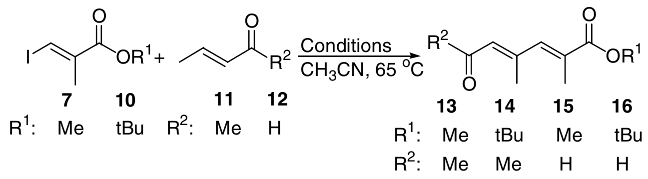
According to the literature,[8a] tetrasubstituted 2,4 ***E***, ***E***-dienedioic acid and their derivatives (Table 1, assuming $R^1 = H$ or Me and $R^2 = OH$ or OMe) have been synthesized via Heck reaction of the corresponding (***E***)-3-bromo-2-methyl acrylic acid or the methyl ester with (***E***)-3-methyl acrylic acid or the methyl ester, whereas a free aldehyde reactant did not give identifiable products in the reaction. To the best of our knowledge, synthesis of potentially useful tetrasubstituted ***E***,***E***-dienones (Table 1, **13** and **14**) or ***E***,***E***-dienals (Table 1, **15** and **16**) has not been reported. While β-bromomethacrylate **6** (Scheme 1)[9] and substituted vinyl ketone **11** (Table 1) have been used in the Heck reactions,[8,10] our initial study of direct coupling between **6** and **11** under the standard Heck reaction condition generated the dioxo-tetrasubstituted dienone **13** in only 18% yield along with unidentified by-products.[11]

In order to improve the yield of this coupling product, the more reactive ***E***-vinyl iodide **7** (Scheme 1) was efficiently prepared. According to the literature,[12] **7** has been synthesized in 44% from diethyl methyl malonate in three operations. In this study, an efficient and high yielding route to the exclusive formation of **7** was developed by a sequential bromination–elimination of dimethyl acrylate **4**, followed by the transhalogenation without the need of column chromatography or distillation after workup (Scheme 1, Eq. 1). This synthesis was facilitated by CuI-mediated transhalogenation[13] of vinyl bromide **6** in DMF in high yield (84%) as well as by using DBU as the base in the elimination step to give a quantitative yield. Interestingly, under the same sequential reaction conditions, though elimination of methyl *tert*-butyl acrylate **5** delivered vinyl bromide **8** in quantitative yield, the transhalogenation of **8** only gave the carboxylic acid **9**[12a] (78%) instead of the desired ***E***-vinyl iodide **10** (Scheme 1, Eq. 2). Employing HMPA at 120 °C with the reduced reagent set (1.7 equiv CuI/



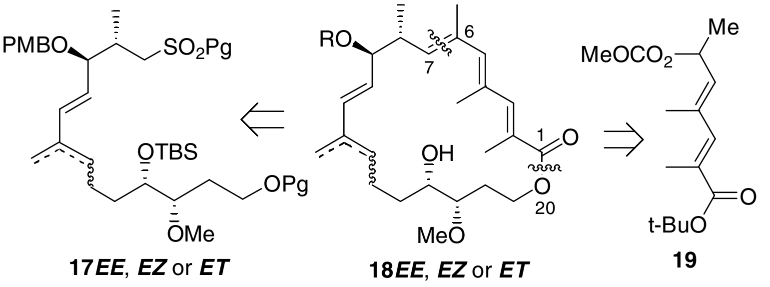
Scheme 1. Synthesis of vinyl iodides **7** and **10**.

Table 1. Overman modified Heck reaction of iodides **7** and **10**[a]

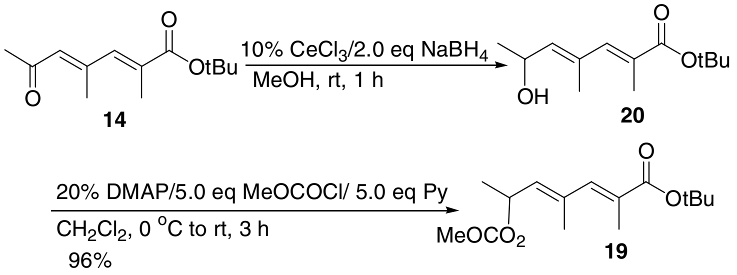


Entry	SM	Reaction conditions	Pdt	Yield (%)
1	**7**	2.0 equiv **11**, 5% $Pd(OAc)_2$, 1.5 equiv Ag_2CO_3, 1 h	**13**	79
2	**10**	2.0 equiv **11**, 5% $Pd(OAc)_2$, 1.5 equiv Ag_2CO_3, 1 h	**14**	75
3	**7**	4.0 equiv **12**, 10% $Pd(OAc)_2$, 2.5 equiv Ag_2CO_3, 8 h	**15**	65
4	**10**	2.0 equiv **12**, 5% $Pd(OAc)_2$, 1.5 equiv Ag_2CO_3, 1 h	**16**	72

[a] All were isolated yields by silica gel column chromatography, **11** was distilled before use, and **12** was directly used as purchased.



Scheme 2. Retrosynthesis of aglycones **18**.



Scheme 3. Synthesis of segment C1–C6 (**19**).

5.0 equiv KI) completely avoided the ester cleavage, and ***E***-vinyl iodide **10** was exclusively formed in 88% yield (Scheme 1, Eq. 3). It should be noted that the reduced reagent set was also applicable for the synthesis of vinyl iodide **7**.

With vinyl iodide **7**, it was found that the coupling of vinyl ketone **11** under Overman modified Heck reaction conditions[14] gave 79% yield of ***E***,***E***-dienone **13** exclusively, where with vinyl iodide **10** the good yield (75%) for ***E***,***E***-dienone **14** was also obtained (Table 1, entries 1 and 2). Extension of the coupling reactions to 2-butenal **12**, a free aldehyde, was found to work fairly well to deliver ***E***, ***E***-dienals **15** (65%) and **16** (72%), respectively (Table 1, entries 3 and 4).

Our approach to the synthesis of apoptolidin (Fig. 1, **1**) is designed to probe the relationship between ring conformation and antineoplastic activity.[4,15] Retrosynthesis envisions that the aglycone **18*EE***, ***EZ*** or ***ET*** will arise from a union of segments C7–C20 (**17**) and C1–C6 (**19**) by Ramberg–Bäcklund reaction[16] with a final ring closure by Yamaguchi macrolactonization,[17] or perhaps via the alternative order (Scheme 2).

Recently, we reported a new three-operation conjunctive strategy towards regio/stereoselective synthesis of **17*EE***, ***EZ*** and ***ET***.[18] In the current study, a concise and efficient preparation of segment **19** is achieved from dienone **14** in two steps (Scheme 3). The regiospecific ketone reduction of **14** was achieved exclusively under Luche reduction condition[19] to give the pure dienol **20** in quantitative yield without the need of column chromatography. Methoxycarboxylation of **20** with methyl chloroformate under reflux in methylene chloride delivered segment C1–C6 (**19**) of apoptolidin in 96% yield (Scheme 3). In addition, X-ray crystallographic analysis of the dienoic acid **21** confirmed the ***E***,***E***-configuration,[20] which was consistent with stereospecificity of the Heck reaction.[8]

In summary, the efficient accessibility for dioxo-tetrasubstituted 2,4 ***E***,***E***-dienes (Scheme 1 and Table 1) and proven amenability of the dioxo functional groups (Scheme 3 and Ref. 20) features a new strategy for constructing tetrasubstituted conjugated dienes in complex compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.058.

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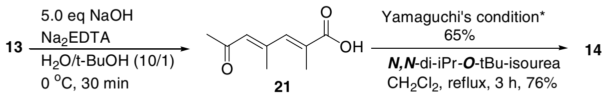
20. In our initial study, it was found that transesterification of dienone **13** to give **14** occurred easily through crystalline dienoic acid **21** under the optimized saponification condition, followed by esterification with mild Yamaguchi's conditions (Ref. 17) or with *N,N* -diisopropyl-*O*-*t*-butylisourea in even better yield.



* a) 1.0 eq 2,4,6-trichlorobenzoyl chloride, THF, rt, 40 min
b) 2.0 eq t-BuOH, 2.0 eq DMAP, toluene, rt, 4 h