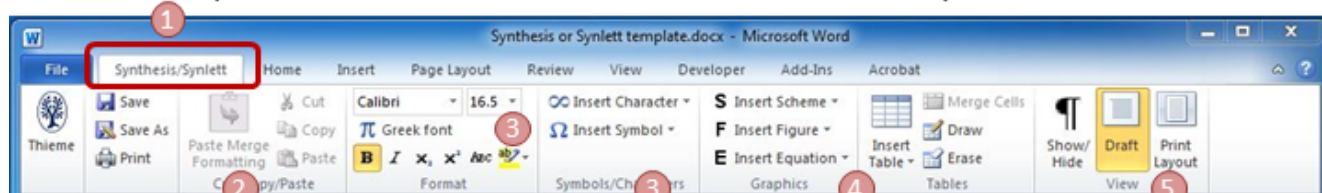


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# Studies towards the synthesis of Tetrodecamycin

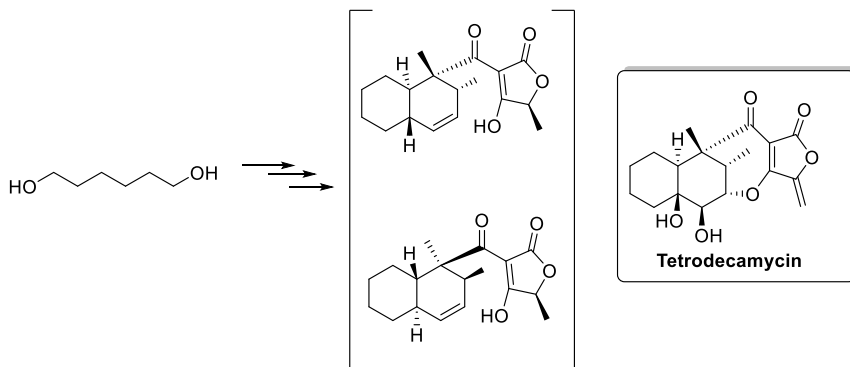
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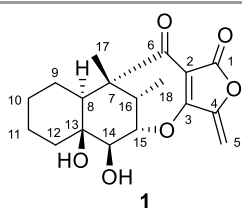


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**Abstract** A studies towards the natural product Tetrodecamycin is reported. A modified Schläpfer Wittig reaction was utilized to prepare the precursor for the subsequent intramolecular Diels-Alder reaction, which delivered the *trans*-decalin ring of the natural product. The tetronic acid moiety was prepared by a Dieckmann reaction and the cyclisation of the tetronic acid to the *trans*-decalin ring was examined.

**Key words** Schläpfer Wittig, Intramolecular Diels-Alder, Aldol, Dieckmann cyclisation, tetronic acid.

Tetrodecamycin (**1**) is an antimicrobial antibiotic that was isolated from a strain of *Streptomyces sp.* MJ885-mF8.<sup>1</sup> (**Figure 1**)



**Figure 1** Tetrodecamycin

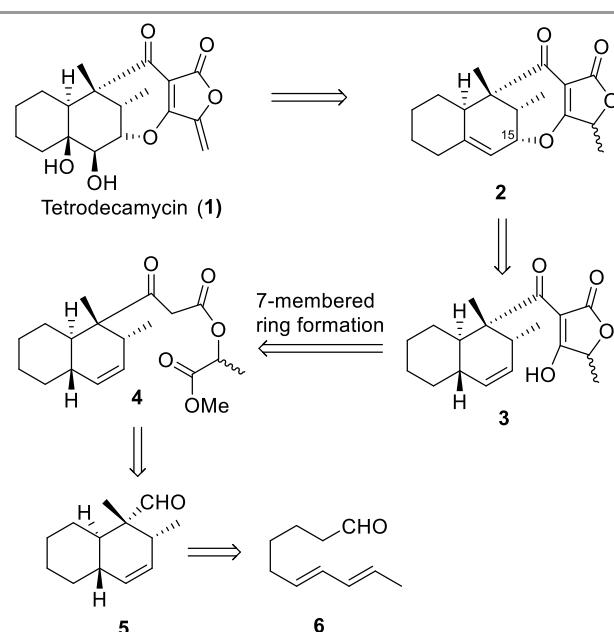
The structure of **1** was subsequently determined by analysis of the NMR data of **1** and its reduced acetyl derivative. The absolute configuration of **1** was established by the modified Mosher's method.<sup>2</sup> The structure of **1** consists of a 6-6-7-5-membered tetracyclic core, one fully and diversely substituted cyclohexane ring in the middle, two quaternary carbons located at C-7 and C-13 with a 2-acyl-4-ylidene tetronic acid derivative portion. (Figure 1)

The interesting structure of **1** and its biological activities has attracted the attention of synthetic chemists. and a number of

reported synthetic studies have appeared in the literature.<sup>3</sup> In 2006, the Tatsuta group reported the total synthesis of **1**<sup>4</sup> and this still remains as the only completed synthesis of this natural product.

We have previously reported the synthesis of a fragment of **1** using silyl enol ether chemistry.<sup>37</sup> Herein, we present the investigation of an alternative approach towards **1**.

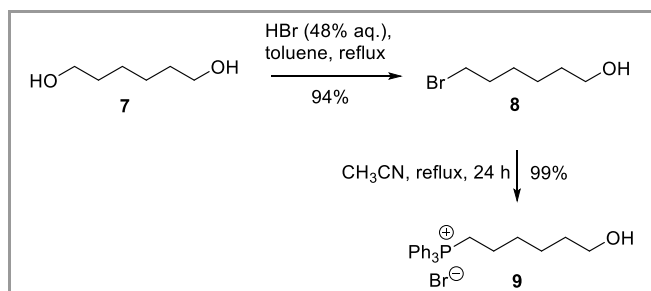
Retrosynthetically, it was envisaged that **1** could be obtained by from **2**. In turns, **2** would be made available by cyclisation of **3**, which came from the Dieckmann cyclisation of **4**. Intermediate **4** could be prepared from decalin aldehyde **5**, which could be obtained from an intramolecular Diels-Alder reaction of **6**.



**Figure 2** Retrosynthetic analysis of Tetrodecamycin (**1**).

The synthesis of **6** was first reported by Snider<sup>5</sup> and subsequently by Paintner group.<sup>3b</sup> Both syntheses utilized the  $\text{Li}_2\text{CuCl}_4$  catalysed cross coupling reactions between protected Grignard reagents and commercially available (2*E*,4*E*)-2,4-hexadien-1-yl acetate for C-C bond formation. Both the Snider and Paintner groups observed low yields for these coupling reactions. Rather than repeating the literature route, we elected to develop a new synthesis of aldehyde **6**.

Treatment of commercially available 1,6-hexanediol **7** with hydrogen bromide (48% aq.) in toluene under reflux afforded monobrominated alcohol **8** in high yield. Reaction of **8** with triphenylphosphine in acetonitrile gave phosphonium salt **9** in almost quantitative yield after overnight reflux. (Scheme 1)



**Scheme 1** Synthesis of phosphonium salt **9**.

Our aim was to conduct a Schlösser modified Wittig reaction<sup>6</sup> of unprotected **9** with aldehyde **10**. A number of factors affect the outcome of a Schlösser Wittig reaction. Extensive investigations by the Schlösser group demonstrated that phenyllithium, preferably “homemade”, is the reagent of choice for the Schlösser Wittig reaction, due to its low tendency to aggregate.<sup>6d</sup> It was also observed that methyllithium gave fairly good performance for the same reaction, despite it exists as a tight tetramer. The amount of lithium salts in the reaction was found to be crucial for achieving stereocontrol. An over-stoichiometric concentration of lithium salts would suppress the dissociation of the  $\alpha$ -lithiated betaine ylide to an  $\alpha$ -metal-free betaine ylide, which would result in the lost in stereoselectivity between *threo* form and *erthro* form of betaine ylide.

Practically the preparation of phenyllithium is hazardous and also it has limited shelf life. Therefore it is relatively inconvenient if one is to conduct the Schlösser Wittig reaction on a large scale. We wondered if the recommended “homemade” phenyllithium in the Schlösser Wittig reaction could be substituted with the commercially available methyllithium.lithium bromide complex. We postulated the addition of an excess lithium salts in the reaction would break up the methyllithium clusters and provide a more reactive organolithium species.

The investigation of the *E*-olefination of phosphonium salt **9** with aldehyde **10** is summarised below.

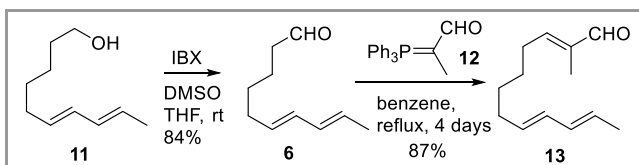
**Table 1** Schlösser Wittig between phosphonium salt **9** and aldehyde **10**.

Entry	Conditions	Yield/%	<i>E/Z</i> ratio
1	MeLi-LiBr <sup>a</sup> (2 eq), THF, -78°C; rt, 30 min; <b>10</b> , -78°C; MeLi-LiBr (1.2 eq), -30°C; rt, 30 min; HCl <sup>c</sup> (1.1 eq), -78°C, 30 min; KO <sup>t</sup> Bu (1.24 eq) -78°C-rt	53	25:1
2	MeLi-LiBr (2 eq), THF, -78°C; rt, 30 min; <b>10</b> , -78°C; MeLi-LiBr (1.2 eq), -78°C; rt, 30 min; CF <sub>3</sub> CO <sub>2</sub> H (1.1 eq), -78°C, 30 min; KO <sup>t</sup> Bu (1.24 eq) -78°C-rt	62	90:10
3	MeLi-LiBr (2 eq), LiCl <sup>b</sup> (3 eq), THF, -78°C; rt, 30 min; <b>10</b> , -78°C; MeLi-LiBr (1.2 eq), -78°C; rt, 30 min; CF <sub>3</sub> CO <sub>2</sub> H (1.1 eq), -78°C, 30 min; KO <sup>t</sup> Bu (1.24 eq) -78°C-rt	71	95:5

a) MeLi-LiBr exists as a 1.5 M solution in Et<sub>2</sub>O. b) Lithium chloride was dried at 150°C *in vacuo* line overnight. c) HCl exists as a 1.0 M solution in Et<sub>2</sub>O; rt = room temperature.

Initially, the double deprotonation of **9** using two equivalence of methyllithium.lithium bromide complex at low temperature followed by stirring at room temperature resulted in the formation of the corresponding ylide. Further deprotonation of the ylide at low temperature using methyllithium.lithium bromide complex followed by reprotonation using HCl in ether and finally addition of potassium *tert*-butoxide gave the desired product **11** in 53% yield with a *E/Z* ratio of 25:1 (Entry 1). We observed that the commercial source of HCl in ether varied in quality and found it affected the consistency of the yield. Therefore trifluoroacetic acid was used as a substitute for HCl in ether. This gave a 62% yield of **11** with an *E/Z* ratio of 90:10 (Entry 2). Finally, inclusion of lithium chloride (three equivalence) and using trifluoroacetic acid as proton source, a 71% yield of **11** was obtained, with a respectable *E/Z* ratio of 95:5. Further investigation will be carried to examine the general applicability of this modified protocol.

Compound **11** was then oxidized with 2-iodoxybenzoic acid (IBX)<sup>7</sup> to aldehyde **6** which was olefinated<sup>8</sup> with ylide **12** to form aldehyde **13**. (Scheme 2)



**Scheme 2** Synthesis of aldehyde **13**.

Next the intramolecular Diels-Alder reaction of **13** was investigated. (Table 2)

**Table 2** Lewis acid mediated intramolecular Diels-Alder reaction of **13**.

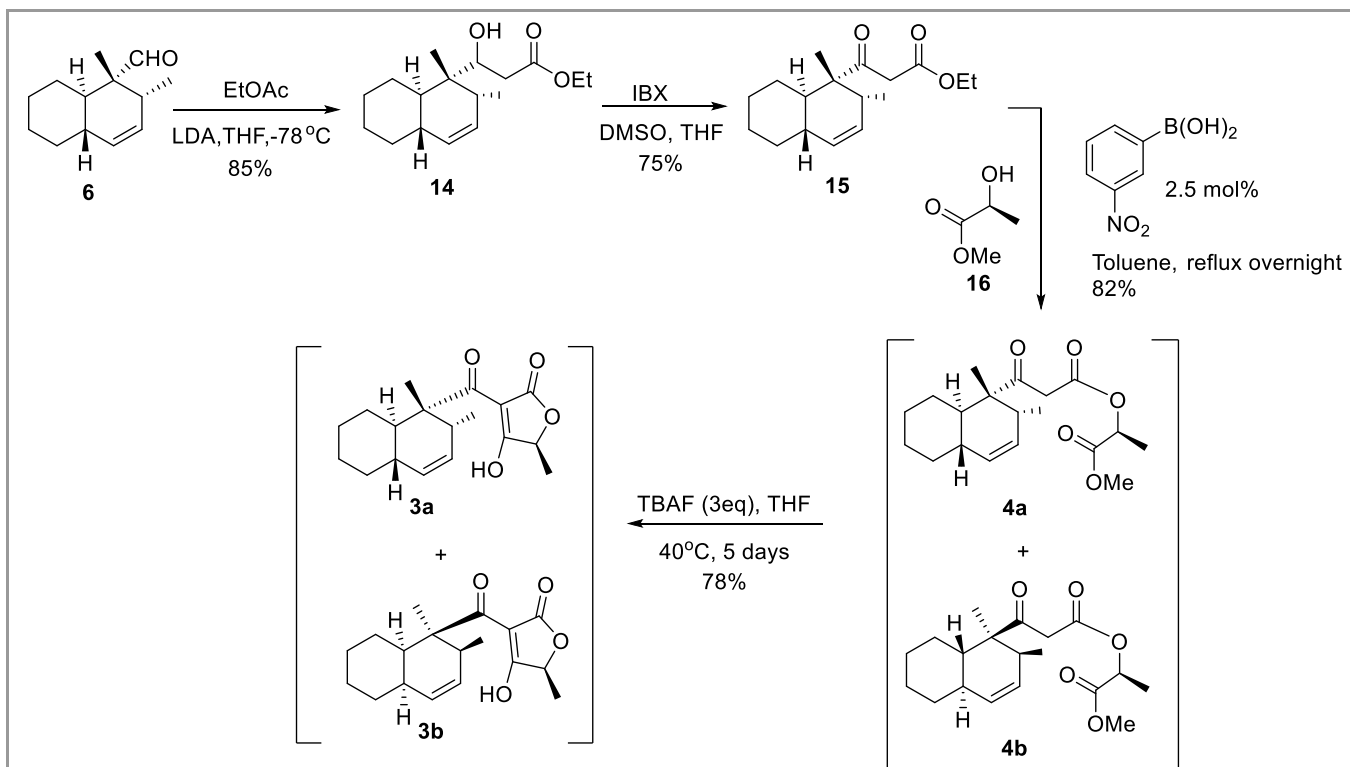
Entry	Conditions	Results
1	Et <sub>2</sub> AlCl (1.3 eq), CH <sub>2</sub> Cl <sub>2</sub> , 0°C, 3 h	Complex mixture
2	Et <sub>2</sub> AlCl (1.02 eq), CH <sub>2</sub> Cl <sub>2</sub> , -78°C, 6 h	Mostly unreacted <b>13</b>
3	Et <sub>2</sub> AlCl (0.95 eq), toluene, -78°C to rt, overnight	Unreacted <b>13</b> + complex mixture
4	ZnCl <sub>2</sub> (1.0 M in THF, 1.2 eq), CH <sub>2</sub> Cl <sub>2</sub> , rt, 3 days	<b>6</b> (25%) + <b>13</b> (53%)
5	ZnCl <sub>2</sub> (1.0 M in Et <sub>2</sub> O, 1.2 eq), CH <sub>2</sub> Cl <sub>2</sub> , rt, 4 days	<b>6</b> (66%)

<sup>a</sup> Insert table footnotes here.

Treatment of **13** with Et<sub>2</sub>AlCl in dichloromethane<sup>8</sup> at 0°C for 3 hours only resulted in the formation of a complex mixture (Entry 1). No reaction was observed when the reaction temperature was lowered to -78°C, despite of prolonged reaction duration (Entry 2). Switching the reaction medium to toluene and gradually raising the reaction temperature again

resulted in the formation of a complex mixture, admixed with unreacted **6** (Entry 3). When ZnCl<sub>2</sub> in tetrahydrofuran was used as Lewis acid,<sup>9</sup> the desired product **6** was formed in 25% together with recovered **15** in 53% after stirring at room temperature for 3 days (Entry 4). Eventually it was discovered that by extending the duration of the ZnCl<sub>2</sub> mediated reaction to four days, a 66% yield of **6** could be obtained (Entry 5).

With the *trans*-decalin framework became available the construction of the tetrone acid moiety was examined. Compound **6** was subjected to an aldol reaction with deprotonated ethyl acetate<sup>10</sup> to afford condensation product **14**. Oxidation of **14** with IBX gave β-keto ester **15** in good yield. A transesterification reaction was performed on **15** with methyl *S*-lactate (**16**), using 3-nitrophenylboronic acid as catalyst,<sup>11</sup> delivered **4a,b** as a diastereomeric mixture. This mixture was not separated but was utilised directly for Dieckmann cyclisation. However, this cyclisation was far from trivial. After examining a number of base/ solvent combinations were examined, eventually it was found that by stirring **4a,b** with tetra-*n*-butylammonium fluoride<sup>12</sup> in THF at 40°C for 5 days, a combined yield of 78% was obtained for tetrone acids **3a,b** (Scheme 3)



**Scheme 1** Synthesis of tetrone acids **3a,b**.

With **19a,b** in available the intramolecular cyclisation to form a seven-membered ring was examined. Attempts to perform a palladium (II) catalysed oxidative cyclisation<sup>13</sup> only resulted in the recovery of starting material. Treatment of **3a,b** with

phenylselenenyl chloride<sup>14</sup> and triethylamine did not induce the expected cyclisation, even after the reaction were left stirring for one week. Again, unreacted **19a,b** was recovered. (Figure 4)

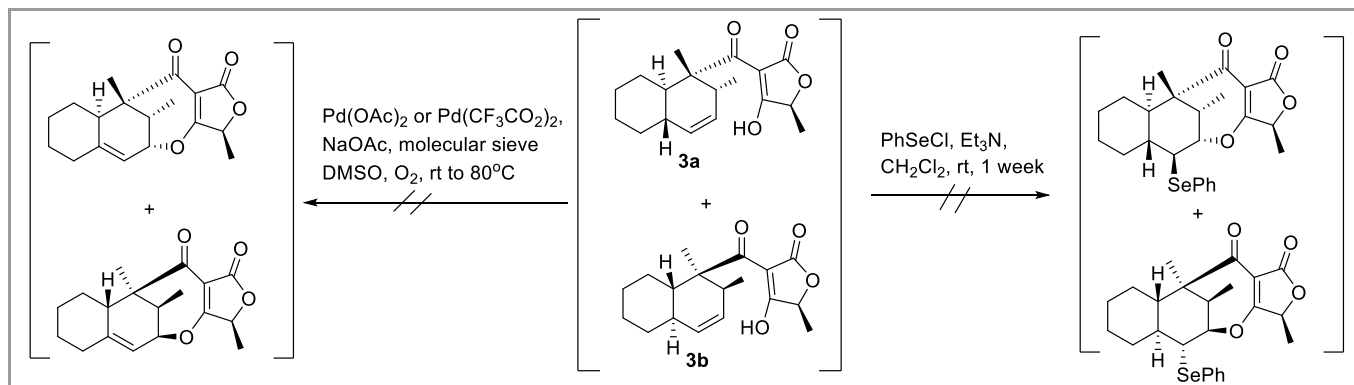


Figure 4 Attempted cyclisation of 3ab.

We speculated that the failure of **3a,b** to undergo cyclisation was partly due to their solubilities but mainly due to the difficulty in the formation of the medium sized seven-membered ring.

In conclusion we have completed the synthesis of the *cis*-decalin and the tetronic acid parts of Tetrodecamycin (**1**). Although we were unable to close the seven-membered ring, this venture allowed us to develop a more practically convenient version of the Schlösser Wittig reaction, which may make the application of this reaction more appealing to other.

### Funding Information

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