## SYNTHESIS AND TRANSANNULAR DIELS-ALDER REACTION OF A 13-MEMBERED MACROCYCLIC TRIENE HAVING A TETRASUBSTITUTED ENOL ETHER AS A DIENOPHILE<sup>#</sup>

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ABSTRACT: Cyclization of TTC allylic chloride 22 gave TTC macrocycle 24 which was directly converted into a mixture of tricycles TST 25 and CSC 26.

In the preceding communications<sup>1,2</sup> we reported that the transannular Diels-Alder reaction on a macrocycle is a potentially powerful strategy for the construction of complex polycyclic molecules. We also described the synthesis and the Diels-Alder reaction of two specific examples, namely a *trans-cis-trans*<sup>1</sup> (TCT) and a *trans-cis-cis*<sup>2</sup> (TCC) 13-membered macrocyclic trienones. In this paper, we wish to report the synthesis and the transannular Diels-Alder reaction of **24** (Scheme 1), a TTC 13-membered macrocyclic triene having a tetrasubstituted enol ether as a dienophile.



**SCHEME 1** ( $Y = CH_2OCH_2C_6H_5$ ,  $X = OCH_2OCH_3$ ,  $E = COOCH_3$ )

<sup>#</sup> This paper is dedicated to Professor Zdenek Valenta on the occasion of his 60th birthday.

The synthesis of the acyclic precursor 22 which has a *cis* dienophile and a *transtrans* diene is summarized in Scheme 2. Emmons-Horner condensation of the known *trans* unsaturated aldehyde 1<sup>3</sup> with ethyl diisopropyl phosphonoacetate<sup>4</sup> gave the expected *trans-trans* conjugated ester 2.<sup>5</sup> The tetrahydropyranyl group was then replaced by a *t*-butyldimethylsilyl protecting group to give diene ester 4. Reduction of 4 with dibal-H gave the corresponding diene alcohol 5 which was converted into the corresponding *trans-trans* allylic chloride 6. Michael addition of dimethyl malonate with methyl vinyl ketone<sup>9</sup> followed by ketalization gave ketal malonate 7. Condensation of the sodium salt of 7 with allylic chloride 6 gave malonate 8 which was converted into benzyl ether derivative 11 by successive decarboethoxylation,<sup>10</sup> reduction with Dibal-H and benzylation.

Mild acid hydrolysis of ketal **11** gave the corresponding ketone allylic alcohol **12** which was reconverted into a *t*-butyldimethylsilyl ether derivative (**13**). Emmons-Horner reaction of the lithium salt of methoxymethyl methyl dimethylphosphonoacetate **14**<sup>11</sup> with **13** gave a 1:1 mixture of *trans* and *cis* unsaturated esters **15** and **16** which on reduction with Dibal-H afforded a mixture of *trans* and *cis* allylic alcohol **17** and **18** which were separated by column chromato-graphy on silica gel. The *cis* allylic alcohol **18** was then converted into the allylic chloride **19** which was alkylated with dimethyl malonate to give **20**. Removal of the silyl ether protecting group and halogenation provided the desired acyclic allylic chloride **22** having a TTC geometry.

When macrocyclization of TTC allylic chloride 22 was attempted, the expected TTC macrocyclic triene 24 was not observed, instead, two tricyclic products resulting from a transannular Diels-Alder reaction were directly isolated. Thus, when crude allylic chloride 22 in DMF was added over 22 h with a syringe pump in a suspension of sodium hydride in THF-DMF (1:1) at 70°C, this provided as major products, the *trans-syn-trans* (TST) and the CSC tricycles 25 and 26 in a 2:1 ratio (>60% yield from 21) which could be separated by chromatography. The structures of tricycles 25 and 26 were established on the basis of their spectroscopic properties.<sup>5</sup> The exact stereostructure of the major isomer 25 was rigorously established by X-ray analysis.<sup>12</sup>

Taking into account that the Diels-Alder reaction must take place via a boat-like transition state, producing an ABC tricycle with ring B in a boat form, molecular models predict that a macrocyclic triene having a *trans,trans* diene and a *cis* dienophile can give two different tricycles having the TST and the CSC stereochemistry. On that basis, the formation of 25 and 26 (Scheme 1) as major products is readily explained. Indeed, TTC macrocyclic triene 24 can either take conformation 24A or 24B, having each a pseudo equatorial benzyloxymethylene group. Conformations 24A and 24B can then undergo a transannular Diels-Alder reaction producing respectively tricycles 25 (TST) and 26 (CSC) in the conformations 25A and 26A having each an equatorial benzyloxymethylene group.

Macrocyclization was also attempted in the TTT series. The *trans-trans*-trans alcohol **17** was transformed into the TTT allylic chloride **23** using a route similar to that used for the preparation of TTC allylic chloride **22** from *cis* alcohol **18**. Using various basic conditions, we were not successful in transforming TTT allylic chloride **23** into the expected TTT macrocycle or tricycles which could derive from it. This result indicates that acyclic triene having the TTT configuration does not easily undergo the macrocyclization step.



(a) NaH,  $(CH_{3}O)_{2}OPCH_{2}COOC_{2}H_{5}$ , THF, 0°C, 2 h (>60%)<sup>4</sup> (b) PPTS, CF\_{3}COOH, MeOH, r.t., 2.5 h (98%)<sup>6</sup> (c) *t*-Bu(CH\_{3})\_{2}SiCl, imidazole, THF, r.t., 1 h<sup>7</sup> (d) Dibal-H, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 45 min (95% from 3) (e) LiCl, collidine, CH\_{3}SO\_{2}Cl, DMF, 0°C, 1 h; r.t., 1 h (85%, crude)<sup>8</sup> (f) 7,<sup>9</sup> NaH, THF, 0°C to r.t., 1 h; add 6, THF/DMF (5:1), 0°C to r.t., 12 h (89%) (g) LiCl, H<sub>2</sub>O-DMF, 165°C, 2.5 h (61%)<sup>10</sup> (h) Dibal-H, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 30 min (82%) (i) NaH, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>Br THF-DMF (5:1), r.t., 17 h (92%) (j) PPTS, H<sub>2</sub>O-acetone, 65°C, 5 h<sup>6</sup> (k) *t*-Bu(CH\_{3})\_{2}SiCl, imidazole, THF, r.t. (97% from 11)<sup>7</sup> (l) 14, *n*-BuLi, toluene, 0°C; add 13 in toluene, 0°C, 30 min; r.t., 150 h (80%, mixture *cis/trans* (1:1))<sup>11</sup> (m) Dibal-H, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 15 min (73%) (n) LiCl, collidine, CH<sub>3</sub>SO<sub>2</sub>Cl, DMF, 0°C to r.t., 1 h (85%)<sup>7</sup> THF-DMF (2:1), 0°C to r.t., 12 h (77% from 18) (p) (*n*Bu)4NF, THF, 0°C to r.t., 1 h (85%)<sup>7</sup>

The Diels-Alder cycloaddition of *cis* and *trans*  $\alpha$ , $\beta$ -unsaturated esters **15** and **16** was also examined in order to obtain a comparison of reactivity between a simple intramolecular (level 1) and a transannular (level 2)<sup>13</sup> Diels-Alder reactions. A mixture of *cis* and *trans*  $\alpha$ , $\beta$ -unsaturated esters **15** and **16** dissolved in toluene was heated at 210°C in a sealed tube during 18 hours. Interestingly, no reaction was observed even though the conjugated tetrasubstituted enol ether of **15** and **16** is considered to be a more reactive dienophile than the non-conjugated one of macrocycle **24**.

In conclusion, this work demonstrates that the transannular Diels-Alder reaction on macrocycles is a powerful synthetic approach because the formation of the tricycle takes place under relatively mild conditions even with a relatively poor diene. The above results also show that

it should be easy to construct tricycles having an alkyl substituent and a hydroxyl group on neighboring carbon atoms at the ring junction (e.g. positions 9 and 10 in steroids). This substitution pattern is found in various natural products like the veratrum alkaloids<sup>14</sup> (cf. germine **27**), batrachotoxinin A **28**,<sup>15</sup> rosenonolactone **29**<sup>16</sup> and forskolin **30**<sup>17</sup> (Scheme 3). The preparation of appropriate key tricyclic intermediates for the synthesis of these natural products via a transannular Diels-Alder reaction on a macrocycle is presently being examined in our laboratory.<sup>18</sup>



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