

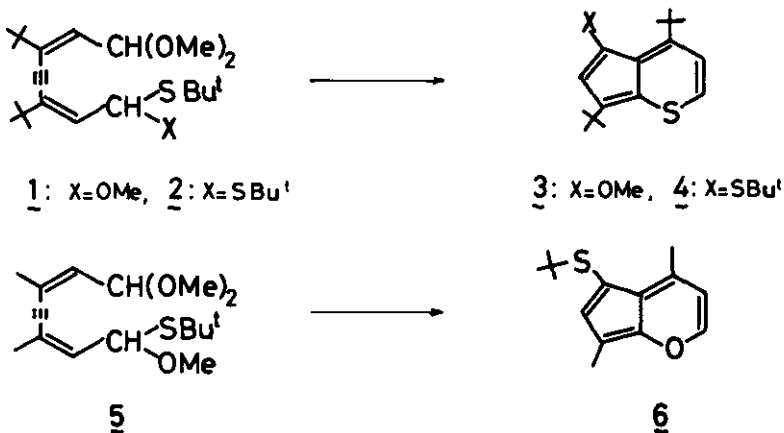
SYNTHESIS AND PROPERTIES OF DERIVATIVES OF CYCLOPENTA[b]PYRAN  
AND CYCLOPENTA[b]THIAPYRAN ISOELECTRONIC WITH AZULENE

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**Abstract** — Cyclopenta[b]pyran and cyclopenta[b]thiapyran derivatives isoelectronic with azulene have been synthesized by intramolecular cyclization of substituted octadienyne-dials. The cyclization reaction of octadienyne-dials proceeds regio-specifically and the formation of cyclopenta[b]pyrans and/or cyclopenta[b]thiapyrans depends on a subtle variety of the reaction conditions.

Recently we have reported the formation of cyclopenta[b]thiapyran derivatives (3 and 4) and cyclopenta[b]pyran (6) by acid-catalyzed intramolecular cyclization<sup>1)</sup>. The results of the X-ray structure analysis of 4 showed the delocalized structure of cyclopenta[b]thiapyran with peripheral 10 $\pi$ -electron system<sup>2)</sup>. In order to clarify the mechanism of this interesting cyclization reaction and to get further information on the properties of these azulene analogues, we have carried out the cyclization of octadienyne-dials bearing different substituent groups.

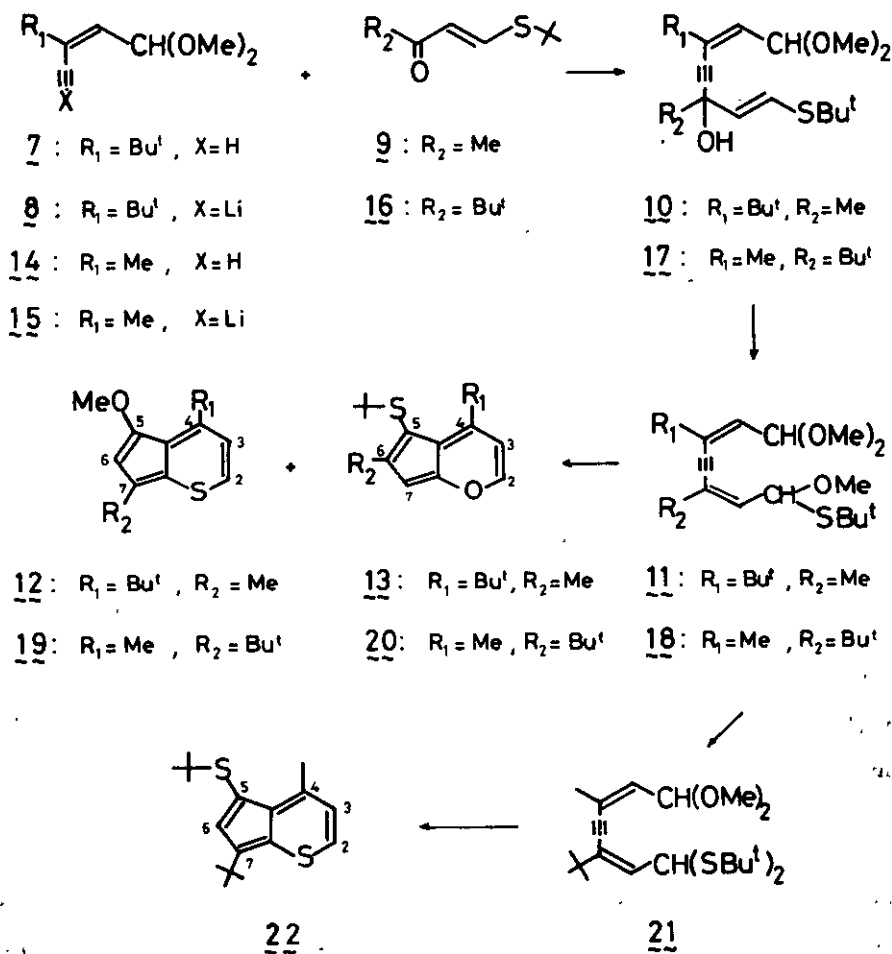


We have prepared two isomeric *t*-butyl methyl derivatives (Scheme 1). The *t*-butyl substituted enynaldehyde dimethyl acetal (**7**)<sup>3</sup> was treated with *n*-BuLi to give the lithio derivative (**8**). The reaction of **8** with methyl thiovinyl ketone (**9**)<sup>4</sup> gave the hydroxy acetal (**10**, yellow viscous oil, 93%). Treatment of **10** (6.46 mmol) with CF<sub>3</sub>COOH (1 ml) - CH(OMe)<sub>3</sub> (50 ml) at -15°C for 2 h gave the acetal-hemithioacetal (**11**, pale yellow viscous oil, 89%). Cyclization of **11** (1.6 mmol) with CF<sub>3</sub>COOH (2.5 ml) - CH(OMe)<sub>3</sub> (10 ml) - CH<sub>2</sub>Cl<sub>2</sub> (50 ml) at -15°C for 20 min gave 4-*t*-butyl-5-methoxy-7-methylcyclopenta[b]thiapyran (**12**, relatively stable deep blue plates, mp 66.7 ~ 69.3°C<sup>5</sup>), 27%; Mass(m/e): 234 (M<sup>+</sup>), 219; <sup>1</sup>H NMR (CCl<sub>4</sub>-acetone-*d*<sub>6</sub>) δ 7.50 d (J=10.0, H<sub>2</sub>), 7.07 d (J=10.0, H<sub>3</sub>), 6.32 s (H<sub>6</sub>), 3.86 s (OCH<sub>3</sub>), 2.22 s (CH<sub>3</sub>), 1.50 s (*t*-Bu); UV: λ<sub>max</sub><sup>cyclohexane</sup> (ε) 268.5 (14,200), 351.5 sh (3,600), 363 (4,200), 375.5 sh (2,950), 633 (624), 670 sh (589) nm. On the other hand, similar treatment of **11** (1.7 mmol) with CF<sub>3</sub>COOH (1 ml) - CH(OMe)<sub>3</sub> (25 ml) - CH<sub>2</sub>Cl<sub>2</sub> (25 ml) at -50 ~ 0°C yielded 0.5% of 4-*t*-butyl-5-*t*-butylthio-6-methylcyclopenta[b]pyran (**13**) as deep red needles, mp 72.6 ~ 75.2°C; Mass(m/e): 276 (M<sup>+</sup>), 219, 187; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 7.66 d (J=5.5, H<sub>2</sub>), 6.62 d (J=5.5, H<sub>3</sub>), 6.18 s (H<sub>7</sub>), 2.54 s (CH<sub>3</sub>), 1.64 s (*t*-Bu), 1.12 s (*S-t*-Bu), but none of the thiapyran (**12**).

The reaction of the lithio derivative (**15**) derived from 3-methyl-2-penten-4-yn-1-al dimethyl acetal (**14**)<sup>6</sup> with *t*-butyl thiovinyl ketone (**16**)<sup>1</sup> afforded the isomeric hydroxy acetal (**17**, yellow viscous oil, 93%). The similar treatment of **17** (8.55 mmol) with CF<sub>3</sub>COOH (1.5 ml) - CH(OMe)<sub>3</sub> (50 ml) at -15°C for 1.5 h gave a mixture of **18** and **20**, which were separated by a column chromatography on alumina: **18**, yellow viscous oil, 83%; 6-*t*-butyl-5-*t*-butylthio-4-methylcyclopenta[b]pyran (**20**, stable red plates, mp 70.9 ~ 73.1°C<sup>5</sup>), 1.5%; Mass(m/e) 276 (M<sup>+</sup>), 219; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 7.59 d (J=5.0, H<sub>2</sub>), 6.23 s (H<sub>7</sub>), 6.20 d (J=5.0, H<sub>3</sub>), 2.95 s (CH<sub>3</sub>), 1.49 s (*t*-Bu), 1.20 s (*S-t*-Bu); UV: λ<sub>max</sub><sup>cyclohexane</sup> (ε) 234 sh (10,600), 268.5 (12,500), 327.5 (10,400), 476.5 (701) nm. Cyclization of **18** (1.58 mmol) with CF<sub>3</sub>COOH (2.5 ml) - CH(OMe)<sub>3</sub> (10 ml) - CH<sub>2</sub>Cl<sub>2</sub> (50 ml) at -15°C for 20 min gave 7-*t*-butyl-5-methoxy-4-methylcyclopenta[b]thiapyran (**19**, stable deep blue plates, mp 95.5 ~ 96.7°C<sup>5</sup>), 49%; Mass(m/e): 234 (M<sup>+</sup>), 219; <sup>1</sup>H NMR (CCl<sub>4</sub>-acetone-*d*<sub>6</sub>) δ 7.32 d (J=9.0, H<sub>2</sub>), 6.61 d (J=9.0, H<sub>3</sub>), 6.23 s (H<sub>6</sub>), 3.81 s (OCH<sub>3</sub>), 2.64 s (CH<sub>3</sub>), 1.38 s (*S-t*-Bu); UV: λ<sub>max</sub><sup>cyclohexane</sup> (ε) 225.5 sh (12,000), 270 sh (12,600), 283 (13,300), 346.5 sh (2,930), 353 (3,140), 367.5 sh (2,280), 599 (620) nm along with a trace amount of **20**. The cyclopenta[b]pyran (**20**) could be obtained as a main product (17%) on treatment of **18** (1.55 mmol) with CF<sub>3</sub>COOH (1 ml) - CH(OMe)<sub>3</sub> (25 ml) - CH<sub>2</sub>Cl<sub>2</sub> (25 ml)

at  $-60 \sim 0^\circ\text{C}$ , and 0.3% of 19 was also obtained as a minor product.

In addition, reaction of 17 (3.82 mmol) with  $\text{CF}_3\text{COOH}$  (1 ml) -  $\text{CH}(\text{OMe})_3$  (5 ml) -  $\text{CH}_2\text{Cl}_2$  (5 ml) in the presence of *t*-butyl mercaptan at  $-50 \sim -15^\circ\text{C}$  gave the acetal-thioacetal (21, yellow viscous oil, 48%). Cyclization of 21 (1.7 mmol) with  $\text{CF}_3\text{COOH}$  (4 ml) -  $\text{CH}(\text{OMe})_3$  (5 ml) -  $\text{CH}_2\text{Cl}_2$  (50 ml) yielded 7-*t*-butyl-5-*t*-butylthio-4-methylcyclopenta[*b*]thiapyran (22, stable deep blue prisms, mp  $105.2 \sim 107.6^\circ\text{C}^5$ ), 66%; Mass(m/e): 292 ( $\text{M}^+$ ), 236, 235;  $^1\text{H NMR}$  (acetone- $d_6$ )  $\delta$  8.04 d (J=9.0,  $\text{H}_2$ ), 7.40 s ( $\text{H}_6$ ), 7.17 d (J=9.0,  $\text{H}_3$ ), 3.18 s ( $\text{CH}_3$ ), 1.47 s (*t*-Bu), 1.20 s (S-*t*-Bu); UV:  $\lambda_{\text{max}}^{\text{cyclohexane}}$  ( $\epsilon$ ) 224.5 (17,400), 289.5 (18,900), 294.5 sh (16,800), 349 (4,240), 556.5 (1,210) nm).



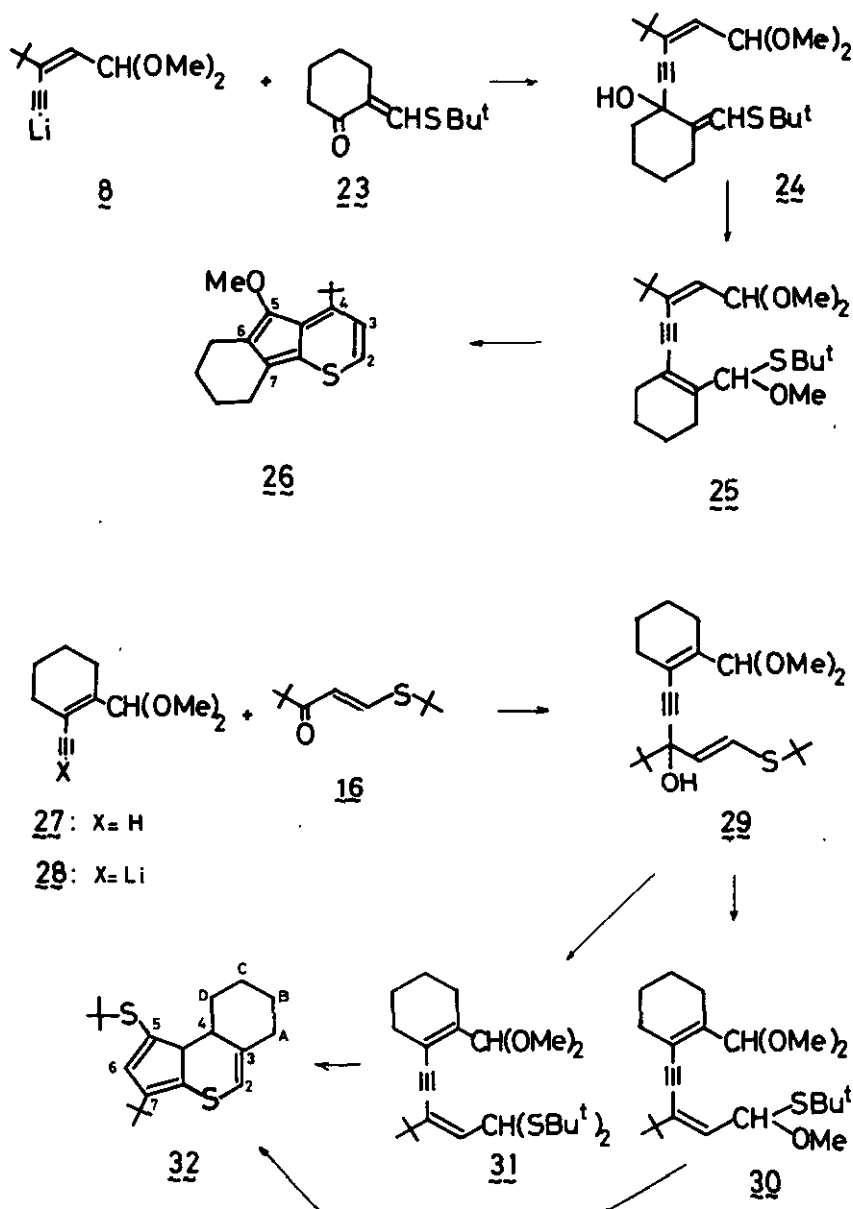
Scheme 1

From these results, the cyclization reaction of the octadienyne-dials bearing *t*-butyl and methyl groups was found to be regiospecific and the formation of cyclopenta[b]pyrans and/or cyclopenta[b]thiapyrans depends on a subtle variety of the reaction conditions. In the case of **11** and **18**, the use of larger amounts of CF<sub>3</sub>COOH and smaller amounts of CH(OMe)<sub>3</sub> leads to the formation of cyclopenta[b]-thiapyrans (**12** and **19**), whereas cyclopenta[b]pyrans (**13** and **20**) are formed by using smaller amounts of CF<sub>3</sub>COOH and larger amounts of CH(OMe)<sub>3</sub>.

In order to obtain further information regarding the mode of cyclization, the same reaction of octadienyne-dial derivatives containing cyclohexene ring was examined (Scheme 2). The reaction of the lithio derivative (**8**) with 2-*t*-butylthiomethylene cyclohexanone (**23**)<sup>7</sup> gave the hydroxy acetal (**24**, pale yellow oil, 95%). The hydroxy acetal (**24**) was converted into the acetal-hemithioacetal (**25**, pale yellow viscous oil, 82%) in the same manner as **10**. Cyclization of **25** with CF<sub>3</sub>COOH-CH(OMe)<sub>3</sub>-CH<sub>2</sub>Cl<sub>2</sub> gave only the cyclopenta[b]thiapyran derivative (**26**). The thiapyran (**26**) formed relatively stable deep blue plates which decomposed during thin-layer chromatography on alumina or silica gel (**26**, mp 102.3 ~ 103.4°C, 35%; Mass (m/e): 274 (M<sup>+</sup>), 259; <sup>1</sup>H NMR (CCl<sub>4</sub>-acetone-*d*<sub>6</sub>) δ 7.62 d (J=9.5, H<sub>2</sub>), 7.21 d (J=9.5, H<sub>3</sub>), 3.88 s (OCH<sub>3</sub>), 2.97 ~ 2.56 m (allylic CH<sub>2</sub>), 1.89 ~ 1.55 m (non-allylic CH<sub>2</sub>), 1.54 s (*t*-Bu); UV: λ<sub>max</sub><sup>cyclohexane</sup> (ε) 239.5 (13,300), 283 (14,000), 356 sh (5,330), 361 (6,980), 387 (4,930), 609 (566) nm). Treatment of **27**<sup>8</sup> with *n*-BuLi followed by reaction with **16** led to the hydroxy acetal (**29**, yellow viscous oil, 98%), which was converted into the acetal-hemithioacetal (**30**, yellow viscous oil, 69%). Under the similar reaction conditions used for **25**, **30** did not yield methoxy derivative, but small amounts of *t*-butylthio derivative (**32**, stable blue prisms, mp 114.8 ~ 115.9°C, 2%, Mass (m/e): 332 (M<sup>+</sup>), 275; <sup>1</sup>H NMR (CCl<sub>4</sub>-acetone-*d*<sub>6</sub>) δ 2.44 br.s (H<sub>2</sub>), 2.71 s (H<sub>6</sub>), 5.95 ~ 6.09 m (H<sub>D</sub>), 7.06 ~ 7.19 m (H<sub>A</sub>), 8.08 ~ 8.25 m (H<sub>B</sub>, H<sub>C</sub>), 8.54 s (*t*-Bu), 8.82 s (*S-t*-Bu); UV: λ<sub>max</sub><sup>cyclohexane</sup> (ε) 217 (19,900), 242.5 sh (13,200), 293.5 (17,300), 353 (4,930), 574.5 (1,240) nm) was obtained. The thiapyran derivative (**32**) could be obtained as a main product from the acetal-thioacetal (**31**) derived from **29**<sup>9</sup>.

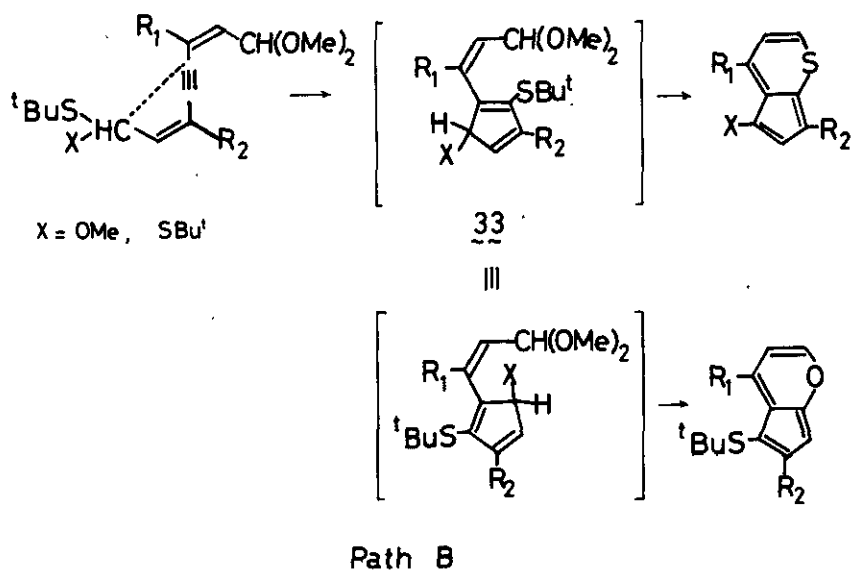
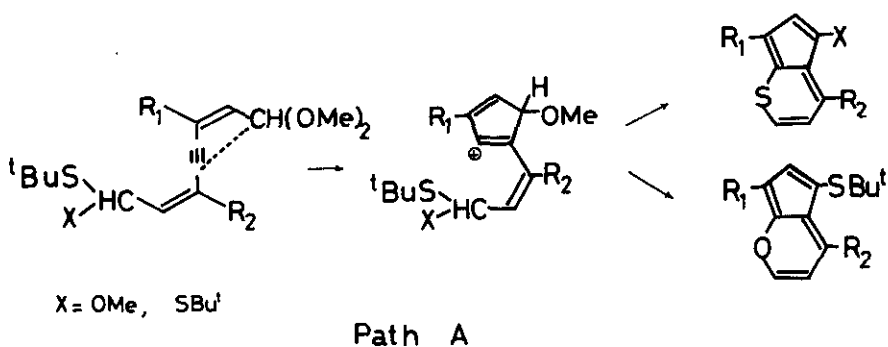
Thus, the formation of cyclopenta[b]thiapyrans and/or cyclopenta[b]pyrans in the acid-catalyzed intramolecular cyclization is influenced by the alkyl substituent groups of the octadienyne-dial derivatives. The cyclization leads to cyclopenta[b]pyran (**6**) when alkyl groups are two methyl substituents (*i.e.*, **5**), whereas cyclopenta[b]thiapyrans (**3**, **4**, **26**, and **32**) are formed when octadienyne-dials bear

two *t*-butyl groups or *t*-butyl group and cyclohexene ring (*i.e.*, 1, 2, 25, 30, and 31). The methyl and *t*-butyl substituted octadienyne-dials (11 and 18) afford both cyclopenta[b]thiapyrans (12 and 19) and cyclopenta[b]pyrans (13 and 20).



Scheme 2

The mechanism of these reactions is not yet completely investigated. A possible pathway is the formation of a five-membered ring with acetal group participation, followed by cyclization to cyclopenta[b]thiapyran and cyclopenta[b]pyran (Path A). However, this path cannot explain the orientation of alkyl groups of cyclopenta[b]thiapyrans (12, 13, 22, 23, and 24) and the formation of 3,5-dialkyl substituted cyclopenta[b]pyrans (6, 13, and 20). To explain the above-mentioned results, we assumed tentatively the formation of an intermediate (33) having cyclopentadiene structure which is formed accompanying a rearrangement of *t*-butylthio group (Path B). Cyclization of 33 with sulfur or oxygen forms cyclopenta[b]thiapyran or



cyclopenta[b]pyran. Further experiments are in progress to elucidate the specific pathways of these interesting novel cyclization reactions.

#### Acknowledgement

The authors would like to thank Professor Ichiro Murata, Osaka University, for his helpful discussions.

#### References and Notes

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- 9) The hydroxy acetal (**29**) was converted into the acetal-thioacetal (**31**) with  $\text{CF}_3\text{COOH}-t\text{-BuSH}-\text{CH}(\text{OMe})_3-\text{CH}_2\text{Cl}_2$  at -60 ~ -50°C for 50 min. **31**, yellow viscous oil, 34%. Cyclization of **31** with  $\text{CF}_3\text{COOH}-\text{CH}(\text{OMe})_3-\text{CH}_2\text{Cl}_2$  at -15°C for 1h gave the thiapyran (**32**) in 28% yield.

Received, 30th September, 1981