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Furanosteroid Studies. Stereoselective Synthesis of the A,B,E-Ring Core of Wortmannin

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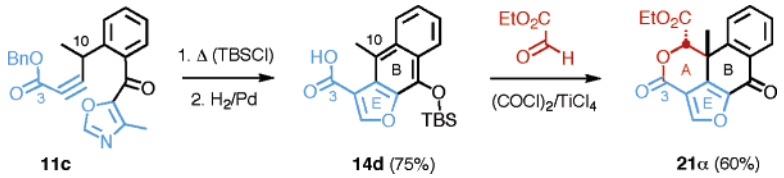
ABSTRACT



11c **14d** (75%) **21α** (60%)

Alkyne oxazole 11c is converted in three steps, and ~45% overall yield, to furanolactone 21α having the A,B,E-ring core of the wortmannin (2) family of furanosteroids. The $TiCl_4$-catalyzed insertion of $EtO_2C–CH=O$ between C_3 and C_{10} in furanoacid 14d is >98% stereoselective via a pathway involving chemoselective lactonization of equilibrating aldol intermediates 23α,β (dynamic kinetic resolution).

The furanosteroids are a class of novel pentacyclic fungal metabolites, characterized in part by a furan ring bridging positions 4 and 6 of the steroid skeleton.[1] Representative examples include members of the viridin (**1**) and wortmannin (**2**) families, distinguished by an aromatic ring C in the former and a strained lactone ring A in the latter (Figure 1).

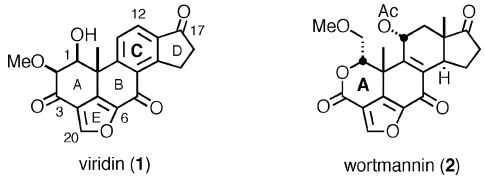


Figure 1. Viridin (**1**) and wortmannin (**2**) furanosteroids.

Viridin (**1**) was the first member of this class to be isolated and characterized (1945),[2a] attracting considerable attention for its potent anti-inflammatory and antibiotic activity. Similar properties were noted for **2** following its structural elucidation in 1968.[2b] However, in recent years, **1** and **2** have become better known for their ability to selectively block certain intracellular signaling pathways, in particular those associated with cell growth and development.[2c,d] A better understanding of such signal disruption might lead to new therapeutic agents for diseases characterized by rapid cell proliferation.

The growth inhibitory properties of **1** and **2** stem partly from their activity as irreversible inhibitors of phosphoinositide 3-kinase (PI3K),[1] a class of enzymes that plays a key role in important cell signaling processes.[2c,d] Also, in an interesting recent development, **2** has been shown to be a potent inhibitor of the mammalian Polo-like kinase PLK1, an enzyme vital to cellular growth cycles that offers a new target in cancer therapy.[2e] Early on it was postulated that inhibition occurs by nucleophilic addition of the kinase to the electron defficient C_{20}-position in **1** and **2**,[3a,b] a hypothesis that was subsequently confirmed by crystallographic studies

(1) For reviews, see: (a) Hanson, J. R. *Nat. Prod. Rep.* **1995**, *12*, 381. (b) Wipf, P.; Halter, J. H. *Org. Biomol. Chem.* **2005**, *3*, 2053.

(2) (a) Brian, P. W.; McGowan, J. C. *Nature (London)* **1945**, *156*, 144. (b) MacMillan, J.; Vanstone, A. E.; Yeboah, S. K. *Chem. Commun.* **1968**, 613. (c) Powis, G.; Bonjouklian, R.; Berggren, M. M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W. F.; Dodge, J. *Cancer Res.* **1994**, *54*, 2419. (d) Ward, S.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, F. *Chem. Biol.* **2003**, *10*, 207, and references cited therein; see also ref 1b. (e) Liu, Y.; Shreder, K. R.; Gai, W.; Corral, S.; Ferris, D. K.; Rosenblum, J. S. *Chem. Biol.* **2005**, *12*, 5256. Wortmannin crystal structures: (f) Petcher, J.; Weber, H.-P.; Kis, Z. *Chem. Commun.* **1972**, 1061. (g) Doi, M.; Ishida, T.; Terashima, A.; Taniguchi, T.; Sasaki, M.; Tanaka, C. *Anal. Sci.* **1998**, *14*, 1191.

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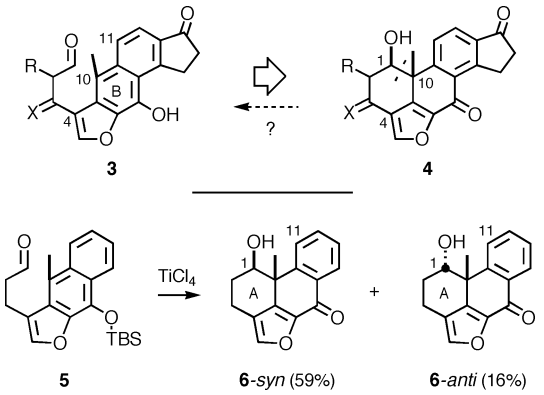
on PI3K-bound **2**.[3c] Surprisingly, though, given the importance of these compounds, synthetic methodology in this area has been relatively slow to develop.[4] Notable achievements include a very elegant total synthesis of **1** by Sorensen et al.[4a] and both formal and total syntheses of **2** by Shibasaki et al.[4b−d]

Recently, we described a new synthetic approach to the viridin (**1**) class of furanosteroids, involving bond disconnection at C_1-C_{10} (cf. **3** → **4** in Scheme 1).[5] The pivital

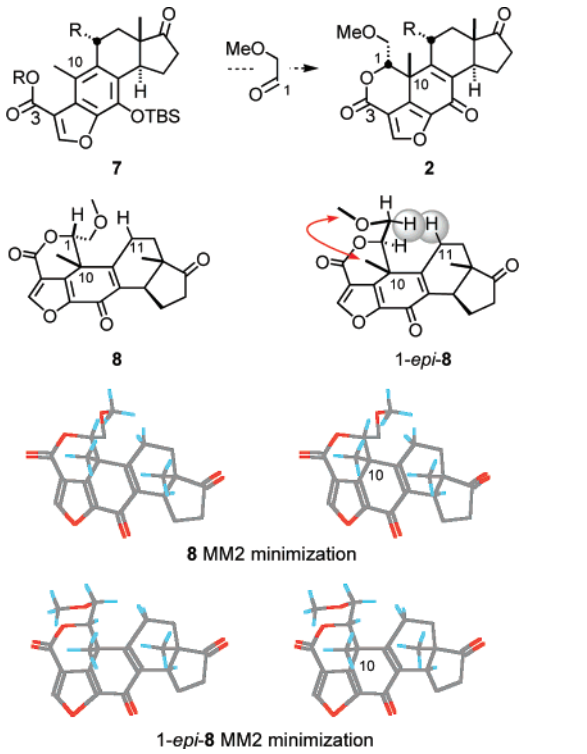
Scheme 1. Viridin (**1**) Synthetic Analysis



step in this strategy requires dearomatization of ring B in **3**, raising the possibility that the reverse process **4** → **3** might be energetically more favorable. However, a search of the literature revealed that simple *retro*-aldol products of type **3** are not known in viridin chemistry. Nor, it appears, are naturally occurring C_1-epimers of **1**,[1−3] although aldol-like equilibration would provide a straightforward pathway for isomerization. We took these observations as evidence of the thermodynamic stability of the C_1-C_{10} bond in **1**, the formation of which relieves strong *peri*-interactions between the coplanar C_4-, C_{10}-, and C_{11}-substituents in open chain species of type **3**.[6] Model studies lent support to this premise. Thus, on $TiCl_4$-catalyzed ring closure, aldehyde **5** was rapidly transformed to a 4:1 mixture of aldol products **6**-*syn*/*anti* in 75% overall yield.[5] Under no circumstances could we detect equilibration between **6**-*syn* and **6**-*anti*.

In principle, a similar strategy might be applied to the synthesis of wortmannin (**2**) and analogues, involving formal insertion of methoxyacetaldehyde or congenors between the C_3-and C_{10}-positions in furanoacid derivatives of type **7** (Scheme 2).[7] However, while in our viridin model studies

Scheme 2. Wortmannin (**2**) Synthetic Analysis



the correct stereochemistry at C_1-C_{10} is kinetically favored by a lower energy Burgi−Dunitz trajectory angle,[5,8] no such bias is likely in the *inter*molecular conversion of **7** to **2**.

Conversely, an argument could be made that the desired *anti*-stereochemistry at C_1-C_{10} would predominate under thermodynamic control, notwithstanding the fact that this geometry corresponds to a 1,2-diaxial orientation (Scheme 2). Taking 11-desacetoxywortmannin (**8**) as an example, models clearly show that the "unnatural" *syn*-isomer 1-*epi*-**8** suffers from steric crowding of two types not found in **8**. One of these is an additional gauche interaction between the C_1-methoxymethyl and C_{10}-methyl groups (curved arrow), while the other corresponds to a strong boat "1,4-flagpole" interaction between the C_1-methoxymethyl and C_{11}-H groups (best seen in the stereoviews derived from MM2 minimization). Calculations at the AM1 level of computation reinforced this analysis, with a 3.6 kcal difference in heat of formation between **8** and 1-*epi*-**8**.[9]

To test this hypothesis, we prepared the model furanoacid derivatives **14a**−**d**, making use of the alkyne oxazole

(3) (a) Wymann, M. P.; Bulgarelli-Leva, G.; Zvelebil, M. J.; Pirola, L.; Vanhaesebroeck, B.; Waterfield, M. D.; Panatotou, G. *Mol. Cell Biol.* **1996**, *16*, 1722. (b) Norman, B. H.; Shih, C.; Toth, J. E.; Ray, J. E.; Dodge, J. A.; Johnson, D. W.; Rutherford, P. G.; Schultz, R. M.; Worzalla, J. F.; Vlahos, C. J. *J. Med. Chem.* **1996**, *39*, 1106. (c) Walker, E. H.; Pacoid, M. E.; Perisic, O.; Stephens, L.; Hawkins, P. T.; Wymann, M. P.; Williams, R. L. *Mol. Cell* **2000**, *6*, 909.

(4) (a) Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1998. (b) Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311. (c) Mizutani, T.; Honzawa, S.; Tosaki, S.-y.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4680. (d) Shigehisa, H.; Mizutani, T.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2005**, *61*, *5057*.

(5) Sessions, E. H.; Jacobi, P. A. *Org. Lett.* **2006**, *8*, 4125.

(6) For related examples, see: (a) Garduno-Ramirez, M. L.; Trejo, A.; Navarro, V.; Bye, R.; Linares, E.; Delgrado, G. *J. Nat. Prod.* **2001**, *64*, 432. (b) Burgueno-Tapia, E.; Bucio, M. A.; Rivera, A.; Joseph-Nathan, P. *J. Nat. Prod.* **2001**, *64*, 518.

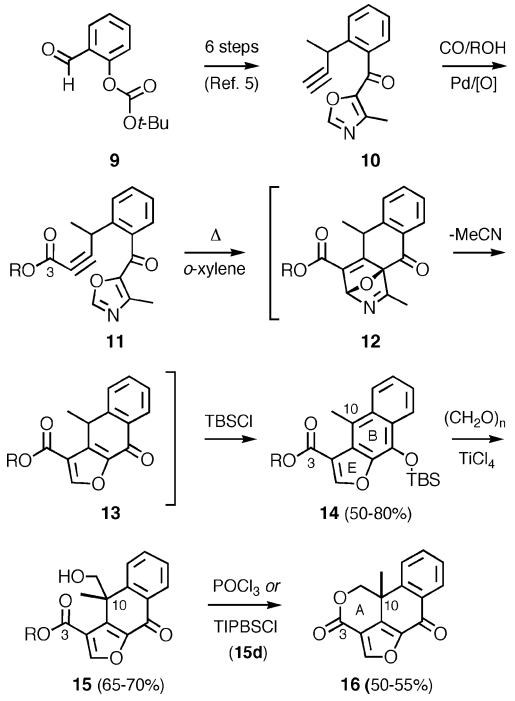
(7) The reverse of this process is known for both **2** and **8** but requires refluxing in 2 N HCl; cf. (a) MacMillan, J.; Simpson, T. J.; Vanstone, A. E.; Yeboah, S. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, *2892*, 2898. (b) Haefliger, W.; Hauser, D. *Helv. Chim. Acta* **1973**, *56*, 2901.

(8) Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

(9) Spartan '02 v1.0.4e (Wavefunction, Inc., Irvine, CA). We are grateful to Professor Dennis Wright (UConn) for carrying out these calculations.

methodology we have employed in the synthesis of numerous naturally occurring furans, butenolides, and lactones (Scheme 3).[10] The requisite Diels−Alder substrates **11a**−**c** were prepared by carboalkoxylation of the terminal alkyne oxazole **10**,[11] itself derived in a very efficient six step sequence beginning with the simple BOC derivative **9**.[5,12] For illustration, alkyne oxazole **11a** (R = Et) was prepared in 70% yield by carboethoxylation of the parent alkyne **10** and gave a 50% yield of the TBS-protected phenol **14a** on thermolysis in *o*-xylene followed by in situ silylation. We were now in position to investigate the vinylogous Mukaiyama-like aldol condensation initiating ring A formation.[13] Ideally, this transformation could be effected with both regio- and stereochemical control, each of which was addressed separately.

Scheme 3. Synthesis of the A,B,E-Ring Core of **2** and **8**



a) R = Et. **b**) R = *t*-Bu. **c**) R = Bn. **d**) R = H.

Our initial investigations were carried out with paraformaldehyde, $(CH_2O)_n$, in order to probe regiochemical control in the absence of stereochemical complications (**14** → **15**, Scheme 3). As in our earlier studies,[5] we expected that dearomatization of ring B would not present a significant thermodynamic barrier. However, the *inter*molecular nature of this reaction introduced additional ambiguity. In the event, we were pleased to find that $TiCl_4$-catalyzed condensation of **14a** with $(CH_2O)_n$ gave a 70% yield of the vinylogous aldol product **15a**, which was reasonably stable to *retro*-aldol cleavage. Also, we found no evidence for attack at other electron-rich positions. Unexpectedly, though, lactonization of **15a** proved to be problematic, likely because of steric crowding in the tetrahedral intermediate leading to **16**, as well as the inherent strain of the furanoisochromene product.[1b] Thus, **15a** was recovered unchanged at temperatures up to 110 °C and suffered decomposition under strongly acidic or basic conditions (method A).

Better results were obtained employing the *tert*-butyl ester **14b**, obtained in 67% yield upon brief heating of alkyne oxazole **11b** in *o*-xylene followed by silylation (method B). On reaction with $(CH_2O)_n/TiCl_4/CH_2Cl_2$, **14b** underwent hydroxymethylation with concomitant ester hydrolysis, affording the corresponding acid derivative **15d** in one step. Due to its instability, purification of **15d** at this stage was not possible. However, treatment of the crude reaction mixture with $POCl_3$/pyridine at rt gave a ∼25% overall yield of the desired wortmannin model substrate **16**.

Finally, a more efficient synthesis of **15d** and **16** made use of the benzyl ester **14c**, obtained in 75−80% yield by thermolysis of alkyne oxazole **11c**. Upon condensation with $(CH_2O)_n/TiCl_4$, **14c** afforded a 67% yield of the readily purified hydroxymethyl derivative **15c** (R = Bn), which on hydrogenolysis gave an 82% yield of acid **15d** in a high state of purity. Treatment of **15d** thus prepared with $POCl_3$/pyridine gave lactone **16** in an improved yield of ∼50% (method C). Alternatively, the reagent system triisopropylbenzenesulfonyl chloride (TIPBSCl)/DMAP in pyridine afforded 54% of **16** (method D). No further efforts were made to optimize this transformation.

We focused on two means for achieving stereochemical control at C_1-C_{10}. The most straightforward of these involved introduction of an epimerizable group at C_1, which on thermodynamic equilibration should greatly favor the desired *anti*-isomer **17**-*anti* (method I, Scheme 4). To explore this route, we carried out the $TiCl_4$-catalyzed condensation of phenol derivative **14c** with ethyl glyoxylate (**18**), which afforded a ∼1:1 mixture of vinylogous aldol products **19**α,*β* as an inseparable mixture. Unlike the case with the simple unsubstituted adducts **15**, these materials were very susceptible to *retro*-aldol reaction and had to be carried forward to lactones **21**α,*β* without purification. This was accomplished in identical fashion to that described in Scheme 3 for **15c**, involving hydrogenolysis to acids **20**α,*β* and lactonization with $POCl_3$ (29% overall yield from **14c**). In each step, the ratio of diastereomeric products remained ∼1:1, indicating that no further equilibration had occurred. Judging from the overall yield, though, it was apparent that significant material had been lost to *retro*-adol cleavage in one or more steps. Also disappointing, we were unable to effect equilibration of **21**α,*β* without significant decomposition. A contributing factor in this difficulty may be the extremely hindered environment of the C_1-H. On a more positive note, though, we did uncover an important clue for further investigation (vide infra).

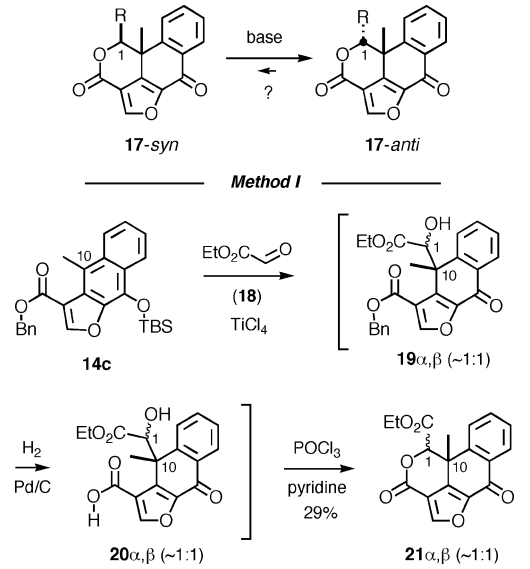
(10) For leading references, see: Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. See also ref 5.

(11) (a) Vedejs, E.; Piotrowski, D. W. *J. Org. Chem.* **1993**, *58* (6), 1341. (b) Izawa, Y.; Shimizu, I.; Yamamato, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2033.

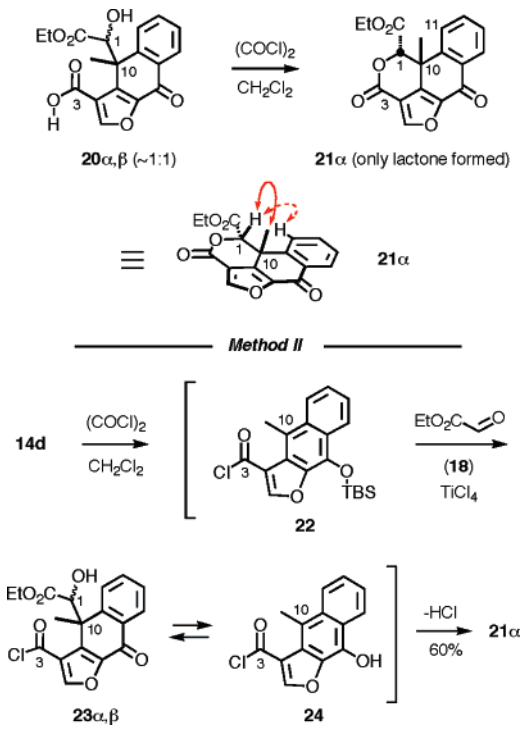
(12) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122* (27), 6502.

(13) For a recent review of this topic, see: Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem.* ***2005***, *117*, 4760.

Scheme 4. Incorporation of an Epimerizable Group at C_1



Scheme 5. (Top) Chemoselective Formation of Lactone **21**α; (Bottom) Stereoselective Introduction of the C_1-Substituent



During our attempts at ring closure of **20**α,*β*, it was nearly always the case that lactones **21**α,*β* were produced in essentially identical ratios to the precursor alcohol-acids **20**α,*β* (NMR). However, one divergent result caught our attention. On treatment of a 1:1 mixture of **20**α,*β* with $(COCl)_2/CH_2Cl_2$ in the *absence* of base, alcohol−acid **20**α underwent chemoselective lactonization to give a modest yield of lactone **21**α as the only identifiable product of ring closure (Scheme 5, top). The structure of **21**α was initially established by NOE studies, which showed a strong correlation between the C_1-H and C_{11}-H as well as the C_1-H and C_{10}-Me group (curved arrows). Subsequent X-ray analysis confirmed this assignment, the solid-state geometry of **21**α closely approximating that predicted computationally for desacetoxywortmannin (**8**) (cf. Scheme 2).[14,15] No evidence could be found for lactonization of **20***β*, whose fate remains unknown (a number of decomposition products indicated that *retro*-aldol cleavage had occurred). Control experiments ruled out the possibility of equilibration of **21***β* to **21**α under the reaction conditions.

An appealing explanation for this observation is that the thermodynamic instability of **21***β* is reflected in the transition state leading from **20***β* to **21***β* (cf. Scheme 2). This would explain why **20***β* suffered intervening decomposition instead of ring closure. Based on this hypothesis, we sought to identify conditions wherein rapid aldol-*retro*-aldol equilibration of **20**α,*β* or a related intermediate might be followed by chemoselective lactonization (method II; dynamic kinetic resolution). Gratifyingly, this was accomplished employing a straightforward modification of our original route (Scheme 5, bottom). Thus, a solution of furanoacid **14d** in CH_2Cl_2 was treated sequentially with $(COCl)_2$ (**14d** → **22**), followed by in situ aldol condensation employing a slight excess of ethyl glyoxylate (**18**)/$TiCl_4$. On stirring at rt one could observe by TLC the very clean formation of lactone **21**α, which was isolated in 60% yield as a colorless crystalline solid (45% overall from alkyne oxazole **11c**). Within the limits of NMR and TLC detection we found no evidence for formation of the epimeric lactone **21***β*.

The level of efficiency in the transformation of **11c** to **21**α is noteworthy, introducing in three steps what are arguably the most challenging structural features found in **2** ("a bisallylic quarternary carbon center and a highly reactive furanocyclohexadienone lactone unit").[4d] The application of this strategy to the synthesis of wortmannin (**2**) and other naturally occurring furanosteroids is under investigation.

Acknowledgment. E.H.S. (Dartmouth College) was the recipient of a National Science Foundation Predoctoral Fellowship during portions of this work. We are grateful to the National Science Foundation, CHE-0646876, for their recent support of these studies.

Supporting Information Available: Experimental and NMR spectra for all new compounds. X-ray crystal structure for **21**α. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We are grateful to Mr. Benjamin E. Kucera and Dr. Victor G. Young, Jr., of the X-ray Crystallographic Laboratory of the University of Minnesota, for performing this analysis and for drawing our attention to the unusual crystal packing geometry found in racemic **21**α.[15]

(15) Racemic **21**α crystallized in a centrosymmetric space group noteworthy for an unusually short intermolecular contact distance between the furan oxygen atoms related by an inversion center (2.64 Å, *in the same range as a medium-strength hydrogen bond*[14]). This appears to be the shortest such furan O−O contact distance reported in the CSD data base (the corresponding distance in monoclinic *C*2 symmetric wortmannin (**2**) is 2.99 Å[18]). The nature of this apparent donor−acceptor interaction will be described separately.