Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1995, **5(2)**, 42–44

Mendeleev
Communications

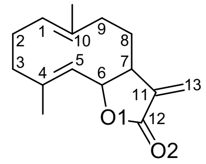
Conformation of the α-Methylene-γ-lactone Ring and Violation of Geissman's Rule in Sesquiterpene Lactones

Koblandy M. Turdybekov,[a] Sergazy M. Adekenov,[a] Victor A. Raldugin,[b] Zeinulla M. Muldakhmetov[a] and Yurii T. Struchkov*[c]

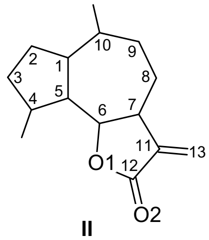
[a]Institute of Organic Synthesis and Coal Chemistry, National Academy of Sciences of Kazakhstan, 470061 Karaganda, Republic of Kazakhstan.
[b]Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 690090 Novosibirsk, Russian Federation.
[c]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation. Fax: +7 095 135 5085

The dependence of the C=C–C=O group chirality on the conformation of the α-methylene-β-lactone ring in sesquiterpene lactones has been established; the known cases in which Geissman's rule is violated are explained by inversion of this ring.

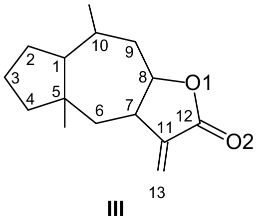
Sesquiterpene β-lactones (STL) are one of the largest classes of natural compound, *viz*. terpenoids. According to the structure of the sesquiterpene skeleton, STL are divided into nineteen structural types.[1] The most widespread among them are germacranolides **I**, guaianolides **II**, pseudoguaianolides **III** and eudesmanolides **IV**. In these STL the β-lactone cycle can be attached either *via* the C6—C7 bond (non-linear lactones) or *via* the C7—C8 bond (linear lactones).



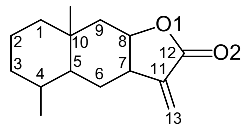
I



II



III



IV

On studying the circular dichroism (CD) spectra of 48 STL, Stocklin, Waddell and Geissman proved that the sign of the Cotton effect (CE) for the $n \rightarrow \pi^*$ chromophore transition of α-methylene-γ-lactones correlates with the type of fusion of the γ-lactone cycle and sesquiterpene skeleton (Geissman's rule) (Table 1).[2]

Table 1 Sign of the CE for the $n \rightarrow \pi^*$ transition of the α-methylene-γ-lactone chromophore in STL.

Fusion bond	Fusion type	
	cis	*trans*
C6–C7	+	–
C7–C8	–	+

Later, it was shown that the sign of the CE for the $n \rightarrow \pi^*$ transition is unambiguously defined by the "chirality" of the C=C–C=O group, *i.e.* by the sign of the C(13)C(11)C(12)O(2) torsion angle. From the results of stereochemical studies on a number of STL with an objectively defined absolute configuration (by anomalous scattering of X-rays by heavy atoms), it has been established that for the α-methylene-γ-lactone ring *trans*-fused *via* the C6–C7 bond the C(13)C(11)C(12)O(2) torsion angle is negative and for those *trans*-fused *via* the C7–C8 bond it is positive.[3,4] It has thereby been shown that an unambiguous dependence between the type of ring fusion, the sign of the torsion angle of the chiral C=C–C=O [C(13)=C(11)–C(12)=O(2)] fragment and the CE sign exists.

However, as mentioned in the paper by Stocklin *et al.*,[2] seven of the 48 STL studied do not obey Geissman's rule. In order to reveal the reasons for this violation, we have analysed in detail the possible conformations of the α-methylene-γ-lactone ring, *trans*- and *cis*-fused with the sesquiterpene skeleton according to the Cambridge Crystallographic Data Base.[5] It has been shown that in most STL the conformation of the γ-lactone ring generally varies from 7α-envelope (7α-E) to 6β,7α-twist (6β,7α-T) (in non-linear STL) and from 7α-E to 7α,8β-T (in linear STL). These conformations can be provisionally called "normal". At the same time alongside "normal" conformations in some STL with *cis*-fusion of carbo- and lactone rings and also in some germacranolides with *trans*-fusion the lactone ring adopts the 6α,7β-T or 7β-E "inverted" conformation. Due to the change of chirality of the C=C–C=O chromophore [*i.e.* the change of the C(13)C(11)C(12)O(2) torsion angle] which occurs on inversion of the α-methylene-γ-lactone ring, this results in a change in the sign of the CE with retention of the ring fusion type, *i.e.* Geissman's rule is violated.

Such an inversion of the lactone ring becomes possible when it is fused to a highly flexible ten-membered ring (as in germacranolides) as compared with *trans*-fusion to significantly less flexible six- and seven-membered rings. Similarly, inversion is also possible when the lactone ring is *cis*-fused with six- or seven-membered rings since these are significantly less fixed. Indeed, among STL that do not conform to Geissman's rule, two are *trans*-fused germacranolides and the rest have *cis*-fusion.

In order to confirm the dependence of the sign of the CE for the $n \rightarrow \pi^*$ C=C–C=O chromophore transition on the lactone ring conformation we have analysed the CD[†] spectra of several available STL and compared them with the known conformation of the α-methylene-γ-lactone ring (according to the X-ray data) (Table 2).

Table 2 CD for the $n \rightarrow \pi^*$ transition of the C=C–C=O chromophore and the conformation of the α-methylene-γ-lactone ring.

Compound	Type of fusion	CE predicted	CE observed λ_{max} (nm), ε		Conformation of lactone ring	C(13)C(11)C(12)O(2) torsion angle/°
			Eudesmanolides			
Pulchelline C (**1**)[7]	*cis*, C7–C8	–	256	−1.1	7,8-T	−10.3
3β-Hydroxy-2α-senecioyl-oxyisoalantolactone (**2**)[8]	*cis*, C7–C8	–	263	−0.9	7,8-T	−19.4
			Guainanolides			
8-Epidesacylcinaropicrine (**3**)[9]	*trans*, C6–C7	–	240	−0.2	6,7-T	−14.1
1,4β-Dioxy-3,10α-dichlor-arglabine (**4**)[10]	*trans*, C6–C7	–	254	−0.7	7-E	−14.2
			Pseudoguaianolides			
Inuchinenolide C (**5**)[7]	*trans*, C7–C8	+	268	0.4	7,8-T	16.9
Britanin (**6**)[8]	*trans*, C7–C8	+	262	0.1	7,8-T	10.6
			Germacranolides			
Hanphilline (**7**)[11]	*trans*, C6–C7	–	265	−0.3	7-E	−13.3
Tamipine (**8**)[12]	*trans*, C7–C8	+	282	0.1	7-E	18.6
Argolide (**9**)[13]	*trans*, C6–C7	–	248–254	+	7-E	10.4
cis, *cis*-Hanphilline (**10**)[14]	*trans*, C6–C7	–	230	0.3	7-E	5.5 (10.9)[a]

[a] Two crystallographically-independent molecules.

As follows from Table 2, there is an agreement between the predicted and observed CE for the compounds **1–8** with the

---

[†] CD spectra were measured by a Spectropol I spectropolarimeter in solutions in ethanol at $T = 22\,^{\circ}$C.

"normal" conformation of an α-methylene-γ-lactone ring. However, for compounds **9** and **10** the observed sign of the CE does not correspond to the expected one and the conformation of the lactone ring is inverted relative to the "normal" one. For all compounds the sign of the CE coincides with the sign of the C(13)C(11)C(12)O(2) torsion angle, because this angle is directly associated with the conformation of the lactone ring.

Thus, it has been experimentally proved that the known violation of Geissman's rule in STL is caused by an inversion of the α-methylene-γ-lactone ring which is possible in germacranolides and when it is *cis*-fused with six- and seven-membered rings.

References

1 K. S. Rybalko, *Prirodnye seskviterpenovye laktony (Natural sesquiterpene lactones)*, Meditsina, Moscow, 1978, p. 320 (in Russian).
2 W. Stocklin, T. G. Waddell and T. A. Geissman, *Tetrahedron*, 1970, **26**, 2397.
3 A. F. Beechman, *Tetrahedron*, 1972, **28**, 5543.
4 A. T. McPhail and G. A. Sim, *Tetrahedron*, 1973, **29**, 1751.
5 Cambridge Crystallographic Database, Release 1989.
6 K. M. Turdybekov, S. V. Lindeman and Yu. T. Struchkov, *Problemy kristallokhimii*, 1992, **9**, 118 (in Russian).
7 S. M. Adekenov, M. A. Abdykalykov, K. M. Turdybekov, Yu. T. Struchkov, A. N. Puschin and N. Yu. Geshtovt, *Khim. Prir. Soedin.*, 1990, 748 [*Chem. Nat. Compd. (Engl. Transl.)*, 1990, 635].
8 S. M. Adekenov, M. Budesinsky, M. A. Abdykalikov, K. M. Turdybekov, D. Samek, E. Bloszyk, B. Drozd and M. Holub, *Collect. Czech. Chem. Commun.*, 1990, **55**, 1568.
9 S. M. Adekenov, G. M. Kadirberlina, K. M. Turdybekov and Yu. T. Struchkov, *Khim. Prir. Soedin.*, 1991, 638 [*Chem. Nat. Compd. (Engl. Transl.)*, 1991, 562].
10 S. M. Adekenov, K. A. Aituganov, K. M. Turdybekov, S. V. Lindeman, Yu. T. Struchkov, I. Yu. Bagryanskaya and Yu. V. Gatilov, *Khim. Prir. Soedin.*, 1991, 33 [*Chem. Nat. Compd. (Engl. Transl.)*, 1991, 27].
11 K. M. Turdybekov, S. M. Adekenov, T. V. Timofeeva, S. V. Lindeman and Yu. T. Struchkov, *Khim. Prir. Soedin.*, 1989, 781 [*Chem. Nat. Compd. (Engl. Transl.)*, 1989, 662].
12 K. M. Turdybekov, S. M. Adekenov, S. V. Lindeman and Yu. T. Struchkov, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.*, 1990, 60 (in Russian).
13 S. M. Adekenov, K. A. Aituganov, K. M. Turdybekov, S. V. Lindeman and Yu. T. Struchkov, *Khim. Prir. Soedin.*, 1991, 653 [*Chem. Nat. Compd. (Engl. Transl.)*, 1991, 575].
14 K. M. Turdybekov, N. M. Gafurov, S. M. Adekenov and Yu. T. Struchkov, *Mendeleev Commun.*, 1994, 81.

Received: Moscow, 16th September 1994
Cambridge, 15th November 1994; Com. 4/05670A