PROBLEM 32

[SUPPL Problem 32 # 2 and 3]

More challenges in Taxane oxetanes

For guidance and inspiration organic scientists devoted to mimicking biosynthesis need to postulate reaction mechanisms presumably occurring within organisms under enzyme governance.

One of the many interesting cases in the taxane area is shown in Scheme SP32.2.1. The backbone rearrangement involved here may mimic Nature’s manner to associate two taxane manifolds since compound II is a diterpene from a Himalayan yew [1]. Would you care to postulate a mechanism? Some stark contrasts with the discussion of TAPSOC problem 32 will emerge as you go along. A feasible mechanism is discussed on next page.

This is a bit challenging. If you feel that this mechanism is still beyond your present possibilities you may leave until after you finish solving up to Problem 60 to get more training. Then, come back here to check how you manage.
Solving Ia → II:

Discernible reactions:

1) Rings A and B contraction. Since this cannot occur simultaneously as would in the case of contraction/expansion of fused rings, there ought to be two tandem rearrangements involved.

2) The Northern C-C bond of gem-dimethyl bridge in I is dislodged and re-bonded involving one of the keto groups, but at this point which one cannot be fingered.

3) The south-eastern oxetane undergoes considerable refurbishing with involvement of benzoate and acetate, probably via neighboring group participation.

4) The only triggering force is the acidic medium, so carbocations are allowed. This opens the way for Wagner-Meerwein rearrangement. As this process leads to another C⁺ which can then mobilize a second rearrangement, a sequence of such bond reorganization can be executed until one decides to kill the C⁺ by elimination or H₂O.

Authors Appendino et al. [1] propose a short sequence that brings about concepts worth commenting.

As you may have surmised, a convenient reaction starter is again located at the bridgehead carbinol despite misgivings discussed earlier. Mind that this C⁺ does not profit from neighboring group stabilization as intermediate 7 (TAPSOCS) does. But there is no escape, accumulation of positive charge on this carbon is mandatory for adequate electron redeployment.

The next step in this design is to perform domino skeletal rearrangements. Fraw your own and see how far you go. Then come back here, please.

Scheme SP32.2.2 (next page, an expanded version of authors’ purported mechanism [1]) portrays the rearrangement cascade:
1) The predicted Wagner-Meerwein rearrangement that explains ring A contraction at the expense of ring B expansion. This is I → IV.

2) But then, electron flow changes dramatically relative to TAPSOC Scheme 32.3 (step 8 → 9 → 10). The α diketone dipole in the northern section changes the direction of electron traffic leading to a benzyl-benzilic acid rearrangement forcing the carbon backbone into a new scaffold: V → VI → II.
Let us add an intriguing note: compound II was the only product (25%) from β-C\textsuperscript{7} hydroxy I\textsubscript{a}, but the α-hydroxy epimer II\textsubscript{b} gave compound VII instead possessing a different scaffold (Scheme SP32.2.3). Can you rationalize this regiochemistry?

\textbf{SCHEME SP32.2.3}

\textit{Solving Ib → VII:}

The apparent change relative to I\textsubscript{a} → II is the attack of the \textit{tert}-carbinol created in V (Scheme SP32.2.2) on carbonyl C\textsuperscript{9} rather than C\textsuperscript{10}. So, the rationale boils down to understanding the influence of the absolute configuration of the C\textsuperscript{7}-OH on the reactivity of either C=O.

Because of the tremendous complexity of these taxanes, it takes a while to get used to the inevitable three dimensional analysis. To this end we must consider intramolecular forces modeling those intermediates preceding the corresponding transition states of the parallel transformations: I\textsubscript{a} → Va → II\textsubscript{a} and Ib → Vb → VII\textsubscript{b} portrayed in Scheme SP32.2.4.

Regarding the progress of I\textsubscript{a} as above, it arrives to Va in which energy minimization (MM2 – TAPSOCS) yields two H-bonds. The first of them involves C\textsuperscript{7}-OH and C\textsuperscript{9}=O, whereas the C\textsuperscript{15} tertiary alcohol limb above the molecular plane is H-bonded to C\textsuperscript{10}=O. Both can be structured at distances typical of H-bonds (see the abridged 3D
structure of Va in Scheme SP32.2.4 – see also inset on black background). This tethering favors the attack of C\textsuperscript{15}-OH on C\textsuperscript{10}=O at an angle of about 105-110° which is perfectly adequate to minimize repulsion from the NBPs of the carbonyl oxygen [2]. Intermediate VIa is thus created which progresses towards end product IIa according to Scheme SP32.2.2 above.

SCHEME SP32.2.4

The 3D model at right (benzoate in the Southern section is not shown for simplicity. The carbonyl and carbinols northern section is emphasized in the orange rectangle. H-bonds are shown in dotted lines, white stronger than blue.
As for the different outcome of enantiomer IIb (→ VII), the primordial singularity is the lack of H bonds of C\textsuperscript{2}-OH with either Northern carbonyls, a situation granting more conformational freedom to ring B (seven membered). In fact, C\textsuperscript{7}-OH becomes H-bonded to the Southern acetate sitting at an accessible distance (183 pm)(Scheme SP32.2.5). Having no competition from C\textsuperscript{7}-OH, the C\textsuperscript{15}-OH has two rotational choices portrayed in the computer-generated models V\textbf{b-1} and V\textbf{b-2}. Observed product VII stems exclusively from V\textbf{b-2} via VIII, a paradox considering the absence of C\textsuperscript{15}-OH---O=C\textsuperscript{9} hydrogen bond (too far) and the expected carbonyl activation from this. See Figure SP32.2.1 for the three dimensional stick models of key intermediates.

Preference for VII may rather be reasoned by comparing the immediate products of cyclizations V\textbf{a} → V\textbf{Ia} vs V\textbf{b} → VIII. While V\textbf{Ia} comports the closing of a five-
membered oxocycle, **VIII** implies cyclization to a six membered ring. In such a congested polycyclic environment this difference may be energetically significant at the \( \Delta H^\circ \) level.

Indeed, molecular mechanics calculations (TAPSOC) give \( \Delta G(\text{VIII} - \text{VIa}) = -53.5 \text{ kcal mol}^{-1} \). Most of this difference occurs in the bending strain energy component. Allowing for some calculation error, such difference on closely related structures is an indication of the much favored cyclization leading to **VIII** and final product **VII** from there. This result suggests late transition states in both cases.

![FIGURE SP32.2.1. Stick models of two rotamers Vb1 and Vb2 discussed around Scheme SP32.2.4. Focus attention on the position of the tertiary carbinol and the conformational changes induced by this minor modification on the rest of the molecule. H-bonds are shown with dotted lines. Notice that Vb2 has only one H-bond.](image)

At the end of the day, the three contributing components for this disparate behavior were:

1. Competition for H-bonding from C\(^7\)-OH and C\(^{15}\)-OH for the \( \alpha \)-diketo moiety
2. Conformational adequacy of the C\(^{15}\)-OH appendage
3.- Product-like transition states and the conformational preference for a six membered- over five membered cyclization.

REFERENCES


[2] The approach of nucleophiles to C=O in addition reactions does not occur necessarily in the perpendicular direction (for max overlap with the p carbon atomic orbital – or the π MO). In fact, an optimal angle of 107º has been estimated. See: Bürgi HB, Dunitz JD, Shefter E. J. Am. Chem. Soc. 1973;95:5065-5067.